BONE SARCOMA

ANATOLE KOLODNY, PH.D., M.D.

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A STUDY OF THE MATERIAL FROM THE REGISTRY OF BONE SARCOMA OF THE AMERICAN COLLEGE OF SURGEONS

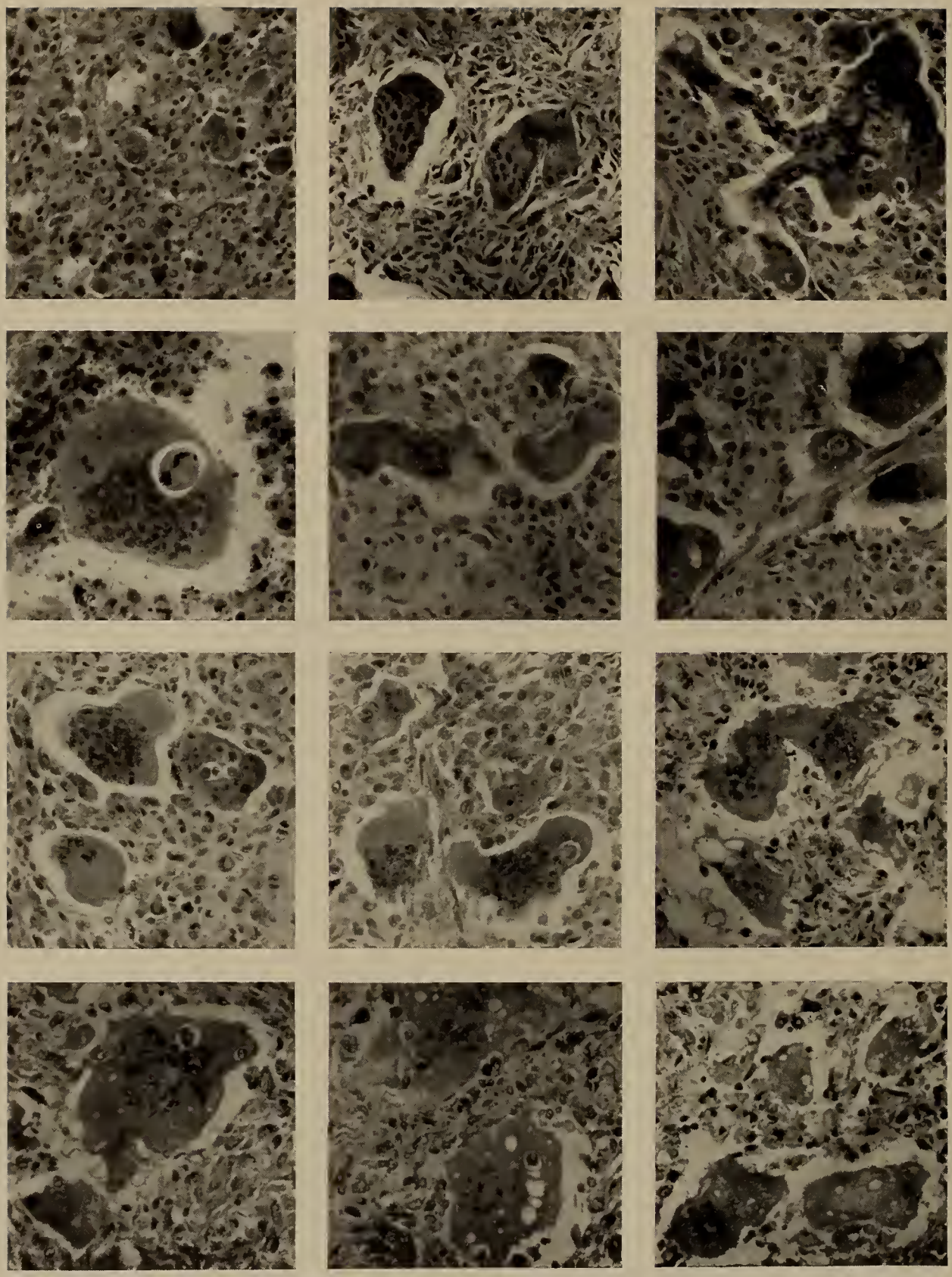

Plate 37. Composed of photomicrographs of cases of giant cell tumor of the Registry collection. Showing vagaries of giant cells of the epulis type. Formation and degeneration of giant cells.

BONE SARCOMA

THE PRIMARY MALIGNANT TUMORS OF BONE AND THE GIANT CELL TUMOR

BY

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Respectfully Dedicated

to

the organizer of the registry of

bone sarcoma of the american college of surgeons

and the first registrar

ERNEST AMORY CODMAN, M.D.

Whose tireless work and

idealism has inspired a generation of students

in their

investigation of bone tumors.

"Where facts are numerous and unquestionable, and unequivocal in their significance, theory must follow them as it best may, keeping time with their step, and not go before them, marching to the sound of its own drum and trumpet."

Oliver Wendell Holmes, 1842

CONTENTS

PREFACE

THE experience of the Registry of Bone Sarcoma of the American College of Surgeons brought much light in the dark field of malignant bone tumors. For various reasons, however, few clinicians and laboratory men have had the opportunity to study the material and to share in the gains of the Registry. It seemed appropriate at this point to assemble, analyze and critically present before the profession at large the multitude of facts and information gained from a personal study of the 700 cases of the Registry and an extensive review of the literature to date. In consequence of these considerations I attempted to facilitate the comprehension of the frequently opposing opinions by presentation of the views at which I arrived after repeated studying of this material. I court no delusion as to the brevity and inadequacy of the discussion of some questions in this treatise; my desire to present only basic and essential facts as gained from the study of the Registry collection is my excuse. My primary aim is to assist the diffusion of the experience of the Registry as it stands today. I entirely agree with Codman when he says that the opinion of one who has studied "this series of cases could certainly be of help to anyone on whom the responsibility of decision of life and limb rests."

In the chapter on classification I am presenting a critical analysis of the classification offered by the Registry Committee and am suggesting certain changes in it. In the chapter on osteogenic sarcoma I have discussed at considerable length the general principles of the pathological diagnosis and prognosis common to all primary malignant bone tumors. Because of the intimate association of the therapy and prognosis of bone sarcoma these two must needs overlap, so that in osteogenic sarcoma both these chapters are best studied together; in the other tumors both these questions are considered in a single chapter.

While the recognition of the benignity of giant cell tumor has had a clarifying influence and while the description of its pathology has contributed much to a better insight into the concept of this disease, the relation of it to malignant bone tumor is still enshrouded in mystery in the minds of the average clinician and pathologist. Multiplicity of causal modalities brings forth identical phenomena and by virtue of overlapping manifestations of varied origin intricate clinical complexes result. Thus lesions of varied motivation must needs be considered in connection with and in relation to malignant tumors that may bring about a similar diagnostic and prognostic issue. I have therefore included in this mono-

graph the giant cell tumor that occasionally calls forth clinical symptoms similar to malignant bone sarcoma.

The illustrations are selected from the material of the Registry. Only a few roentgenograms are brought in of cases observed by me elsewhere. Not all of the roentgenograms of the Registry chosen to serve as illustrations are irreprehensible from the standpoint of technique; in many instances the technical points essential for a satisfactory reproduction of the roentgenogram had been neglected.

It is a pleasure to give acknowledgment to all those who in this country and in Canada have helped me in securing the roentgenograms for illustrations. I am greatly obliged to Drs. Codman and Ewing for many valuable suggestions. Thanks are due my chief, Dr. Rowan, without whose support it would have hardly been possible for me to give this study the necessary amount of time and work. I am glad to accord credit to Drs. Beye and Baxter who kindly read parts of the manuscript.

ANATOLE KOLODNY.

INTRODUCTION

THROUGH the irony of fate the case which led to the organization of the Registry of Bone Sarcoma proved to be a carcinomatous skeletal metastatic lesion. This error is not surprising when one realizes that according to experienced observers at the time of the organization of the Registry in 1920 in about half of all cases diagnosed by the clinician and pathologist as bone sarcoma the diagnosis was erroneous. At that time the necessity of a collective study of the primary malignant bone tumors, maladies so rarely diagnosed correctly, became clear to Codman. Experience and accumulation of data were needed to study the natural history of this disease and to test the value of the various therapeutic measures. A narrow road was ahead of the Registry. While in most diseases with a grave prognosis the histological information is secured from the postmortem examination, in bone sarcoma we have had, in the majority of cases, an amputation or exploratory specimen on which to base our diagnosis during the life of the patient. This fact together with the characteristic temptation to prognosticate the outcome of the case stimulates an effort to trace back the clinical history for diagnostic signs and symptoms for future guidance. Independent of the diagnosis and prognosis given by the Registry the individual case goes on its natural course and the outcome frequently demonstrates the diagnostic and prognostic error of the Registry leaders. Experience is the main asset of the physician and none is so valuable as that acquired by mistakes and errors in judgment. The work of the Registry based upon a study of a wealth of material unequaled in the history of bone tumors has accomplished an immense destructive and constructive task. The numerous various classifications of artificially segregated types and varieties of bone tumors suggested in the literature have been carefully considered and in the main have been rejected and an attempt was made to offer a basis for a new standard classification. The widespread idea of the sanctity and invulnerability of the pathological diagnosis was undermined and the importance of the clinical and radiological findings stressed. The benignity of the giant cell tumor constantly questioned by the amputating surgeon was definitely proved and the necessity of conservative treatment advocated. The subject of bone sarcoma was freed of many misconceptions in the literature filled with statistical data of hundreds of cases of "bone sarcoma," cured by various therapeutic methods.

It would be erroneous, however, to shut our eyes on all the blanks in our knowledge of this most important subject even though it has been studied for six

years by a most efficacious collective method. Much remains to be learned of the pathology and histogenesis of such important lesions as Ewing's sarcoma or giant cell tumor. In the study of these tumors no use has been made as yet of modern methods of hæmatology, tissue cultures, and vital staining which promise much. Our knowledge of the histogenesis of normal bone marrow leaves much to be desired. Even less have we learned of the purely clinical side of the problem; we must have the courage to confess our failure as yet to master these diseases. The treatment of bone sarcoma is just a part of the most important and live problem in medicine today of combating the malignant tumors. The uncertainty of cure of bone sarcoma by any method, the variety of form, both in relative pathological activity, in clinical location and superimposed changes are sufficient to stir one's interest for purely scientific reasons, not to speak of the outstanding clinical importance of the subject.

HISTORY

THE word "sarcoma" belongs to those time-honored terms which are enjoying free general usage in medicine despite the fact that they do not at the present express the original idea suggested by the sponsors of the term. The name sarcoma has been used to designate a tumor with a firm and fleshy feel. The conception of sarcoma a century ago was very wide including all tumors that could not be grouped with other tumors belonging to the few separate entities known at that time. Curiously enough with such a wide conception of sarcoma the tumors known today as bone sarcomata were not included in this group. The superficial gross characteristics of these tumors led to the acquisition for them of such names as fungus, exostosis, tophus, osteoma, and bone cancer. Even Virchow who brought light in most of the dark fields of pathological anatomy and who was the first definitely to separate these sarcomata in a special chapter of oncology did not discriminate sharply enough between sarcoma of bone and cancer. It was Boyer who in 1845 christened these tumors with a name which was destined to follow the development of the knowledge of them up until this day. When at about that time a histological trend of study was directed toward malignant tumors, Virchow described the morphology of sarcoma of bone with clarity and detail surprising for that time. A few years later Robin made an attempt to describe two types of bone marrow cells from which bone tumors originate: the myeloplacque, identified by later investigators as the osteoclast, and the medullocell, later osteoblast. Notwithstanding the confusion by Robin of bone forming and blood forming cellular elements, his was an important step forward in the study of bone tumors; and in the renowned monograph of Nélaton of 1860 the author stressed the importance of the discrimination between the *tumeur à myéloplaques* which is clinically benign and the malignant *tumeur à médullocelles*. These correspond to what we know today as giant cell tumor and osteogenic sarcoma. When a few years later Billroth made the erroneous statement denying the clinical and prognostic importance of the histological peculiarities of sarcoma, Gross (1879) severely criticized him in a brilliant monograph on *Sarcoma of the Long Bones* in which he also emphatically stressed the usual benign course of the sarcomata with a giant cell structure. Years have passed during which the knowledge of malignant bone tumors was at a standstill. Then came the illustrious work of Ewing tending to coordinate the clinical and laboratory sides of the question. In America, Ewing, among pathologists, and Bloodgood, among clinicians, have brought it about that the

giant cell sarcomata of bone have been segregated in a separate sharply defined clinical entity as a benign condition. To do away entirely with the term sarcoma in this disease, the latter was named giant cell tumor. About six years ago on the initiative of the ingenious Codman there came into existence the famous Registry of Bone Sarcoma of the American College of Surgeons which has greatly fostered the study of malignant bone tumors. Today the knowledge of bone sarcoma is yet somewhat nebulous and far from being accurate. The treatment of patients with these diseases is still a matter of ardent discussion and study. On the most important chapter on the origin of these tumors today there is only a dim light. Much is left to be learned in this truly virgin field of science.

ETIOLOGY

IT is a surprising failure of oncology that the knowledge of the etiology of tumors is far behind our knowledge of their structure and natural life. Numerous new theories have been evolved during the last hundred years, many of them purely scholastic inventions without any actual facts to support them. Is there any wonder when old theories which have exterminated themselves because of lack of confirmation are brought to life over and over again under different names? Among the factors underlying this failure are the attempts of pathologists to create theories which would explain the origin of all tumors, whether benign or malignant, carcinomatous or sarcomatous. A study of the clinical and pathological nature of a neoplasm suggests that the etiology of each neoplastic entity is probably specific. It is apparent that Ribbert's theory of the displacement of tissue complexes which explains well enough certain tumors, fails in explaining those numerous instances of tumor growth which follow upon irritation. Opening his famous address on genesis of tumors, Billroth said: "Ueber die letzten Ursachen der Dinge nicht nachzudenken, ist im gewissen Sinne ein beneidenswertes Glueck." No theory explains more than the other; none completely satisfies the inquisitive mind. Whatever theory is favored we cannot free ourselves of the acceptance of a constitutional disposition for tumors. In the course of time the hypothesis of a general disposition of the organism to blastomatosis has been generally conceded.

The etiology of the group of bone tumors known as bone sarcoma has frequently been linked with trauma. Whatever the personal views of the investigator as to the etiology of tumors in general may be, it cannot be denied that trauma seems to be frequently associated with the origin of bone sarcoma. Because of the wide difference in definition of trauma by various pathologists the literature is discrepant in statistics about the clinical incidence and the etiological importance of trauma. The leading question suggesting itself is: "What is the relation between the trauma and the appearance of the tumor?" Refraining from a discussion of the many hypotheses of purely philosophical nature, which lack actual basis, I will outline here the belief to which one is inclined after a study of the osteogenic sarcoma group of the Registry material.

In studying a large series of osteogenic sarcoma one cannot fail to be impressed with the fact that all instances of this tumor may be arranged in series in such a way that at one end will be a mass resembling callus, as we see it after fracture, and at the other a most cellular, highly malignant looking osteo-

genic sarcoma. Cases of osteogenic sarcoma may be identified when the bone absorption, new bone formation, and the vascularity can hardly be told from callus in various stages of bone repair. This observation leads one to believe that the development of osteogenic sarcoma is guided by the same principal laws of growth that are usually observed in the animal organism when in the stage of natural growth or when repair and regeneration are on hand. The main and important specific condition required for the development of an osteogenic sarcoma is a stimulus to growth.

From the fertilized ovum the growth capacity is transferred to the animal tissue cells. As long as the organism is in a stage of physiological development, the cells grow without additional stimuli from the outside. But when the growing organism has reached its adult age—the terminal stage of physical development—the growth tendency of the tissue cells is rapidly interfered with, so that no advanced growth is possible. It is a result of what is known as "growth restraint." The enormous rôle of growth restraint is readily understood when one thinks what would become of the animal organism if growth were not interfered with. The tissue cells in adult organisms do not lose their growth abilities, the latter having merely changed from actual kinetic to potential. On this potential growth ability of tissue cells is based the whole process of tissue regeneration and repair. No life would be possible if the potential growth ability of tissue cells to multiply when repair is needed were lost. Trauma with the consequent necessity of repair leads to a temporary change of the potential growth ability to kinetic, i.e., it leads to a temporary elimination of growth restraint in the traumatized region. In some instances, in the presence of rare predisposing factors which are not understood, trauma may lead to a complete loss of growth restraint in the injured organ. The physiologically accelerated regenerative processes may lead then to a violent multiplication of mesoblastic cellular elements which have entirely lost their main object—physiological repair. The continuous multiplication of as yet undifferentiated cells may be followed by dissemination throughout the organism and by the whole characteristic picture of metastasis of a malignant growth. Regeneration and repair are the main but not only effects of trauma, which have some relation to the etiology of tumors. Separation and isolation of cell complexes, hæmorrhage with conseqeunt absorption and encapsulation, necrosis of tissue—they all play an important part in the etiology of mesoblastic tumors, when brought together with predisposing factors.

Thus it is believed that sarcoma of bone is frequently a result of a loss of growth restraint following an accidental or occupational trauma to a previously normal bone or a surgical trauma to an existing benign bone tumor growth. Not infrequently when the tumor appeared immediately after the trauma or when the primary tumor was noticed after a trauma but not long before a generaliza-

tion of the disease was seen, it is probable that the tumor existed long before the trauma and the latter merely led to the discovery of it or an exacerbation of its growth. The mooted question, not how often sarcoma has a trauma history but how frequently a trauma is followed by sarcoma adds to the discredit of the importance of trauma as an adjuvant etiological factor in an organism predisposed to blastomatosis.

CLASSIFICATION

A SATISFACTORY classification of a disease is the main step to an acquisition of knowledge of it. No science is possible if no uniform language and terminology exist. The lack of progress in the knowledge of bone sarcoma in the last decades is not surprising when one realizes the vast number of various names used for bone sarcoma in different countries, in different centers of the same country, and even by different persons in the same institution. The establishment and propagation of a classification of primary sarcomatous tumors of bone is not merely a responsible but also a most difficult task. As in any other branch of science, there are in the knowledge of these tumors certain time-honored prejudices which have been and still continue to be spread among the workers in this field. A name or an idea, however wrong it may be, is difficult to eradicate if it has decades of history behind it. Furthermore a classification will be of practical value only if it is really accessible to the average clinician or laboratory man. This is especially true in bone sarcoma, a condition with a relatively rare clinical incidence.

Two temptations are presented to anyone who is working on a classification of bone tumors. On one hand there is always a desire to be as complete as possible in the classification, so that no bone tumor would be left in the same group with tumors of a slightly different variety, anatomical or clinical. On the other hand one is tempted to sacrifice preciseness for the sake of simplicity. There have been many victims of this last trend of thought. Billroth was one of them when he said: "The subdivisions made according to the histological peculiarities of the various sarcomata, are of no great value during life." It is a matter of fact that no ideal classification of bone tumors is possible with our present-day limited knowledge of their origin and natural history. Every bone tumor is specific in some way or other, and a classification based upon a distinction of the individual fine points would defeat its purpose by the abundance of groups, types, and varieties, which would vary also with the opinion of each expert.

It is not my intention to offer here a new classification. The classification of the Registry of Bone Sarcoma is the best among the prevailing ones. A study of the Registry material, however, suggests certain changes in this classification. The apparently bizarre fact that the Registry material suggests a classification differing from the one accepted by the Registry Committee can be explained by several factors. In the first place the classification of the Registry was accepted

by the Registry Committee when only a limited number of cases were as yet registered and available for study. In the second place the Registry classification was suggested by a Committee composed largely of laboratory men, hence the presence in it of anatomical points of interest without clinical sequence. Further the purpose of the Registry being the study of all bone lesions diagnosed by anyone as bone sarcoma, the Registry classification includes all pathological conditions of bone and not merely primary malignant bone tumors. In the following, the desirable changes in the Registry classification will be brought out by way of a review and critical analysis of it.

The classification accepted by the Registry Committee embraces all bone lesions under eight headings.

1. Metastatic tumors primary in tissues other than bone.
2. Periosteal fibrosarcoma.
3. Osteogenic tumors, (*a*) benign and (*b*) malignant.
4. Inflammatory conditions.
5. Benign giant cell tumors.
6. Angiomata, (*a*) benign and (*b*) malignant.
7. Ewing's tumor.
8. Myeloma.

Since in the present writing only primary sarcomatous bone tumors are dealt with, the following headings alone will be discussed: Heading 2 (periosteal fibrosarcoma), heading 3 subdivision *b* (malignant osteogenic tumors), heading 6 (angioma), heading 7 (Ewing's tumor), and heading 8 (myeloma). The conditions under heading 1, not being primary lesions, and those under heading 4 and the subdivision *a* of heading 3 being essentially benign conditions, will be touched upon merely insofar as it will be necessary to emphasize the clinical, roentgenological, and pathological points characterizing sarcomatous structures as contrasted with these conditions. The benign giant cell tumors will be dealt with separately. To make the matter clearer, the present analysis begins with malignant osteogenic tumors.

The old term osteosarcoma still prevails in the continental literature, where all sarcomatous tumors of bone are embraced under this name. Osteosarcoma, as used in Europe, does not leave out myeloma, Ewing's tumor, and even giant cell tumor, which are all clearly separate clinical and pathological entities. Like "bone sarcoma," osteosarcoma is a collective name which should not be used in the medical literature when scientifically more precise terms are possible today.

Ewing is responsible for the term "osteogenic sarcoma." All primary sarcomatous tumors of bone which do not belong in any of the other groups of the Registry classification are to be referred to osteogenic sarcomata. "Osteogenic sarcoma" includes mainly the lesions which have been known for long as "perios-

teal bone sarcoma," a term which has spread in this country since the days of Gross, and which does not stand a critical analysis as will be brought out later. In free translation osteogenic means derived from bone. The true meaning, however, of osteogenic sarcoma as understood by those who accept the Registry nomenclature is a sarcomatous tumor derived from ancestors of cells which, when duly differentiated, are known as osteoblasts. An osteogenic sarcoma thus is an osteoblastoma, somewhat as a carcinoma of the skin is an epithelioma. Of course, there is a difference in this analogy between osteoblastoma and epithelioma. While in the latter the epithelial cells composing it are more or less typical and duly differentiated, in an osteogenic sarcoma various stages of development of osteoblasts can be seen, from a simple spindle cell to mucoid, cartilage, and even true bone cells.

Simple and clear as this conception of osteogenic sarcoma is, it is of the utmost importance. It involves a series of questions of primary significance for the etiology and pathology of these tumors. Recently in the French literature opposition was raised against this conception of "osteosarcoma" as the authors call these tumors. Departing from a discussion of questions of physiological ossification and the subsidiary rôle of the osteoblasts in it the authors arrive at a modern conception of osteosarcoma. According to their views these tumors are not osteoblastomata, but sarcomata of the connective tissue cellular elements present in the bone and bone marrow. Thus, no difference is to be encountered between a sarcoma of bone and a sarcoma of a fascia. Modern as this conception is it is contrary to well known facts. The authors have seemingly neglected the fact that pulmonary metastases of osteogenic sarcoma show tumor cells, cartilage, myxomatous tissue, and even bone. Since it is impossible to presume that all the numerous metastatic foci have originated from embryological inclusions of which each contained cells of every variety (myxomatous, cartilaginous, and bone), this fact proves that the tumor cells brought through the vascular system from the primary focus into the lungs have retained the ability of the osteoblasts to differentiate in mucoid, cartilage, or bone cells.

A mistake made very frequently is to understand under osteogenic sarcoma a tumor producing bone. An osteogenic sarcoma does not necessarily mean a tumor in which the tumor cells are forming bone. Production of bone is merely a potential ability of the tumor cells. If the tumor is slow growing and the differentiation of the tumor cells is well expressed they may reach the ultimate goal and become bone cells, otherwise the differentiation may desert them halfway, and they are left as mucoid or cartilaginous cells. They may even remain permanently in their primary stage of spindle cells without any definite arrangement and visible aim. While the tumor cells are undifferentiated and rapidly multiplying they affect a corrosive action upon the involved bone. The bone melts away under the approach of the tumor cell. Later on differentiation of

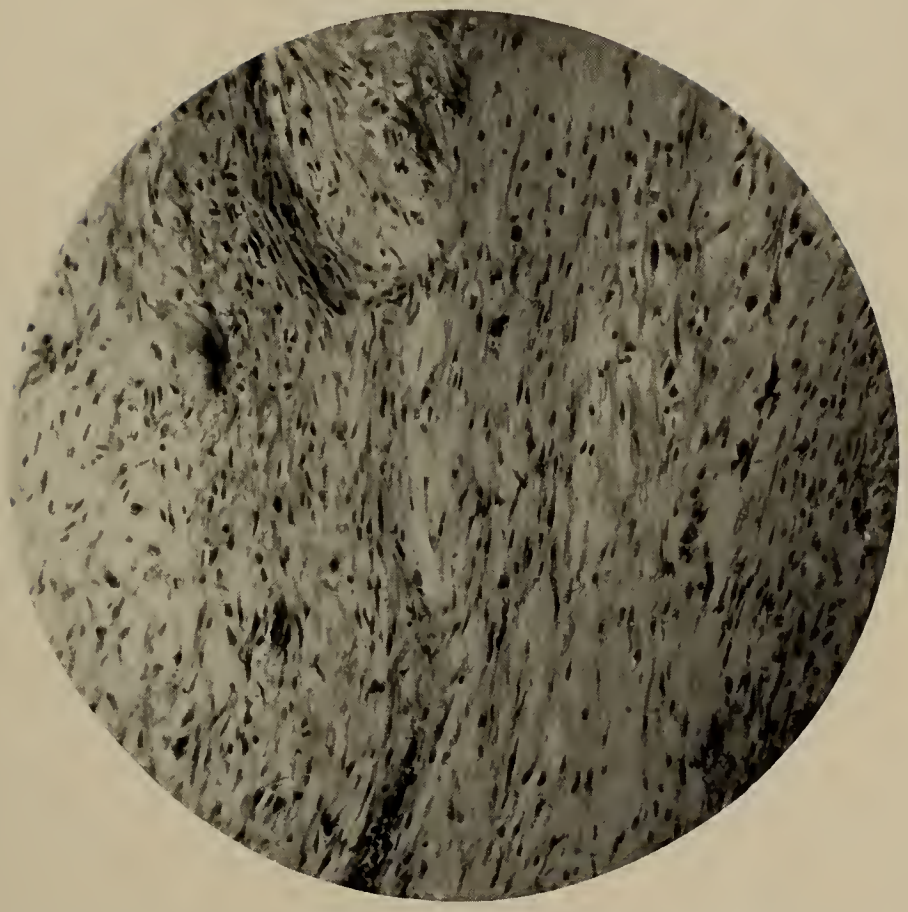


Fig. 1. Case 312.[1] Osteogenic sarcoma. Photomicrograph of a section taken from the same tumor as in Figures 2 and 3. An area showing the structure of a fibrosarcoma.

the tumor cells leads to bone production, but at the same time the undifferentiated tumor areas continue to destroy bone. It is analogous to physiological bone repair in fractures. The first stage of healing of a fracture is the resorption of the bony spicules and the jagged edges of the fragments. Formation of osteoid tissue with calcification is the next stage, when the provisional callus is formed. Then follows the third stage of resorption and consolidation of the exuberant callus. In non-union of fractures, because of local reasons or constitutional disorders the cellular elements which have been called to activity by the law of repair do not differentiate in bone. They remain at the stage of cartilage or myxomatous tissue or even a fibrous septum is left in the line of fracture.

The subdivision of osteogenic sarcoma in various groups and varieties is an exceedingly difficult task. It is obvious that the single criterion of whether a certain peculiarity of a group of tumors is to be sufficient reason for an exclusion of the group in a separate variety or type, is whether or not this peculiarity influences the clinical course of the tumors. Tumors with a histology which

[1] Most of the illustrations are made from material selected from the Registry of Bone Sarcoma of the American College of Surgeons, and the case numbers all refer to the cases recorded in that Registry. Illustrations taken from other sources are so indicated.

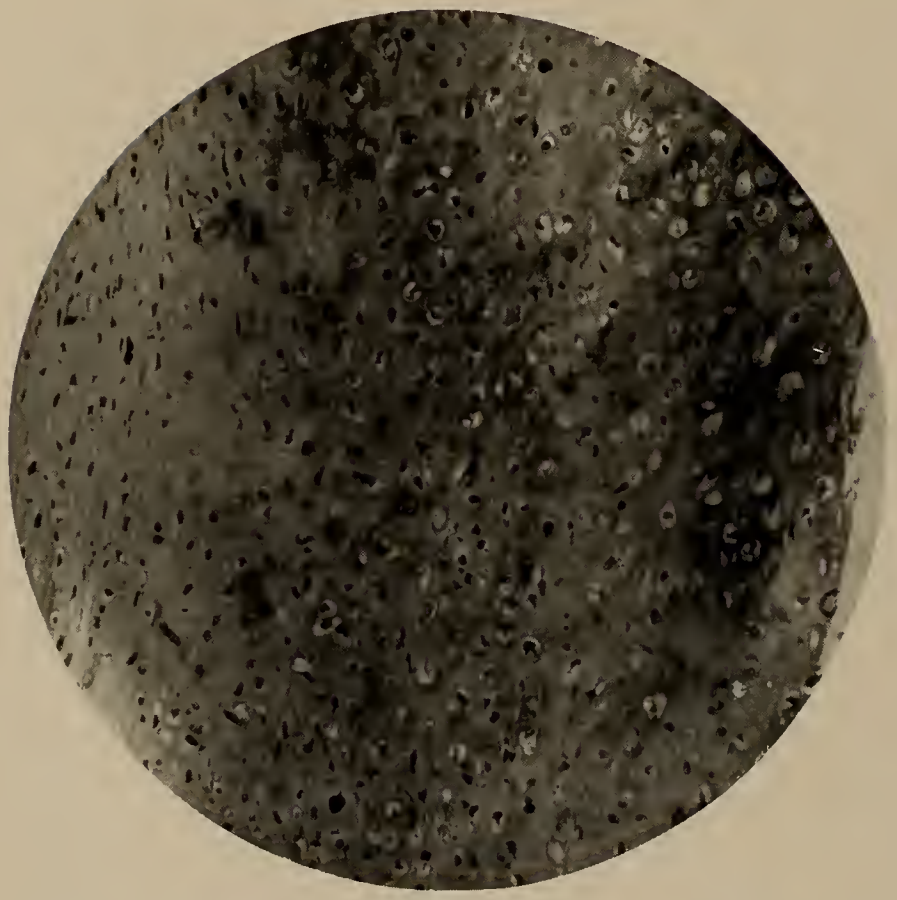


Fig. 2. Case 312. Osteogenic sarcoma. Compare with Figures 1 and 3. An area showing atypical cartilage.

seems to influence their prognosis are apparently entitled to be carried as a special variety or type, separately from the main bulk of tumors. The influence of the structure of the tumor upon the mortality and prognosis and therapy is the only indication for a practical and sound subdivision.

There has long been felt a tendency among students to differentiate sarcomatous tumors according to the variety of the tumor cells and the preponderating tissue which the tumor imitated. Naming tumors on the basis of the features of their cells is inaccurate, because such names do not convey any data of diagnostic importance. Round celled, spindle celled, giant celled sarcomata—they all originate from mesoblastic elements and unless information is furnished as to their origin and clinical peculiarities, these terms are mere sounds lacking any diagnostic and prognostic enlightenment. Naming osteogenic sarcoma according to the specific tissues which the tumor is imitating is also of questionable value. The majority of osteogenic sarcomata studied show a conglomeration of various tissues of mesoblastic origin. If one is not satisfied in the examination of an osteogenic sarcoma by a few sections of one area and one makes an exhaustive study of the whole tumor, one rarely if ever fails to encounter all or several of these tissues (Figs. 1, 2, 3). In one tumor fibrous tissue will predominate, in

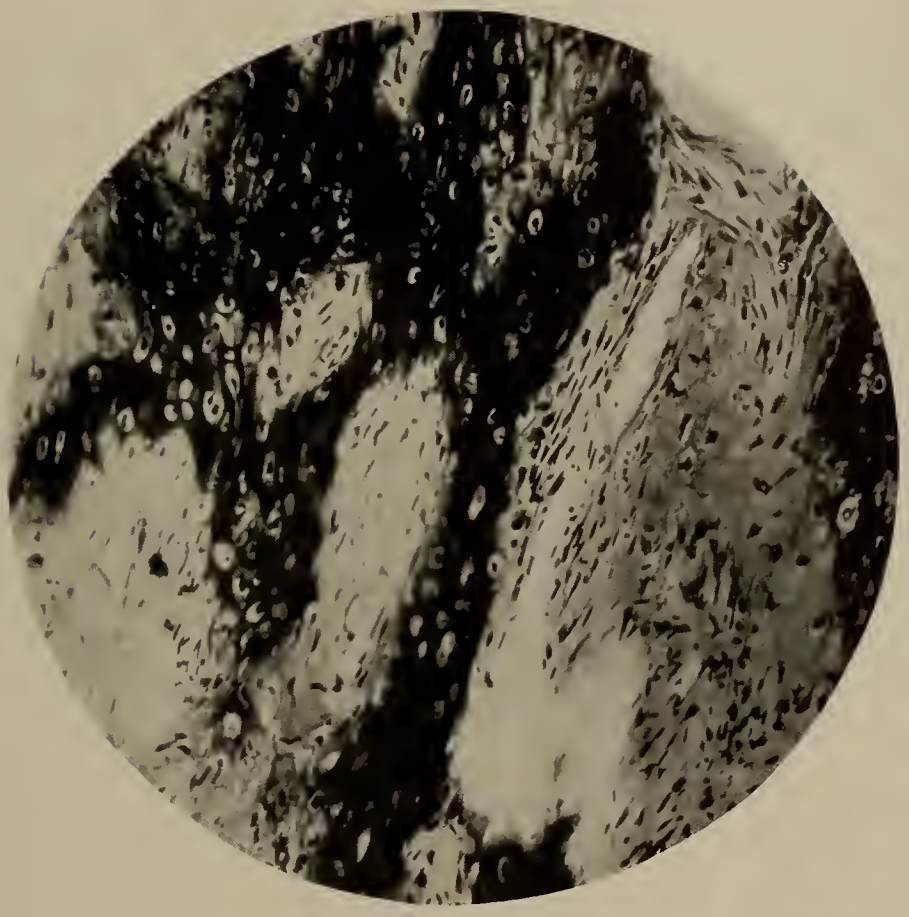


Fig. 3. Case 312. Osteogenic sarcoma. Compare with Figures 1 and 2. An area showing low grade bone formation in a cellular tumor.

another osteoid, in still another myxomatous, and in others chondromatous or osseous tissue will preponderate. A diagnosis including a combination of all or several of these tissues preceding the words "osteogenic sarcoma," merely adds to the mystery with which bone tumors are surrounded. They fall short as far as enlightenment on the clinical and pathological diagnosis and prognosis is concerned.

From the tissue complexes which are found in osteogenic sarcoma, myxomatous tissue has enjoyed the greatest independence in the past. Ribbert in Europe and Bloodgood in America have consistently intimated that myxoma belongs to a separate anatomical entity with a specific origin. Ribbert insists that myxoma is not a product of degeneration of a higher grade tissue since similar degenerations are unknown in normal life and therefore cannot be expected in tumors. However, there is on hand sufficient evidence against the independence of myxomatous parts of osteogenic sarcomata. The myxomatous tissue there is merely a phase of differentiation of the mesoblastic elements which are the progenitors of osteogenic sarcoma. A typical fibroma on one hand and chondroma on the other are almost always encountered along with the occurrence of myxoma.

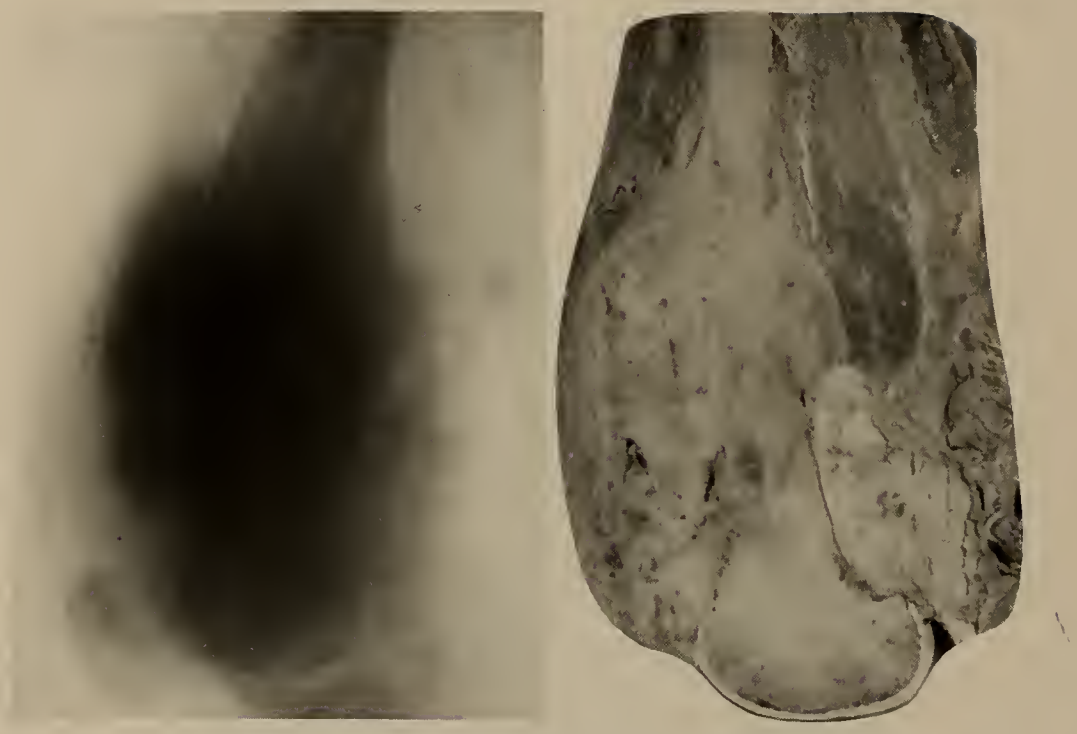


Plate 1. Case 571. See Figure 6. Osteogenic sarcoma in a woman 25 years old. Illustrating the inadvisability of differentiation of periosteal, subperiosteal, and medullary osteogenic sarcomata. The tumor involves the entire transverse diameter of the bone and also surrounds the bone extraperiosteally.

The alleged poorer prognosis of myxoma as contended by Bloodgood is probably due to technical difficulties of eradication of these tumors and not due to their higher potential malignancy. A chemical analysis of myxoma demonstrates the relationship of these tumors to chondromata. Since both myxomata and chondromata yield mucilaginous protein which on hydrolysis yields sulphuric acid and glucosamine (chondroitin-sulphuric acid) they should be related.

The Registry classification recognizes four anatomical types of osteogenic sarcoma: (1) The periosteal, (2) the medullary and subperiosteal, (3) the sclerosing, and (4) the telangiectatic. The spokesman of the Registry, Codman, doubts the advisability of this differentiation, but Ewing, after whose ideas the Registry classification is framed, urges this subdivision because these types are supposed to differ in their gross anatomy, in their microscopic picture, and in their clinical course. From an analysis of Ewing's views as far as the periosteal and the subperiosteal and medullary types are concerned a different conclusion is arrived at. These types are evidently grossly anatomical and the main feature which separates these two groups, as one can judge from the names, is the position in the bone, whether periosteal or subperiosteal. It is obvious that this distinction is valueless as far as clinical diagnosis goes. To state that the exact location of a tumor is periosteal as opposed to subperiosteal and medullary is clinically impossible. To depend for such purposes on the roentgenogram is

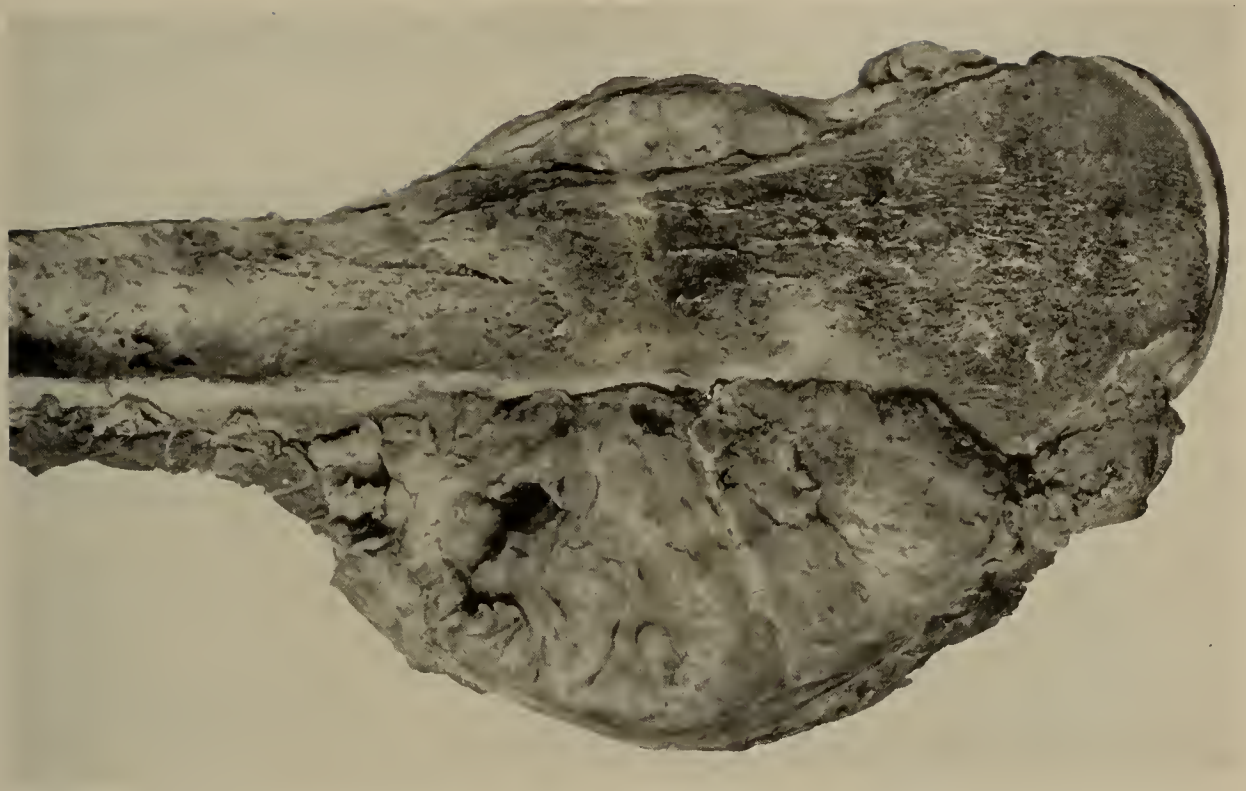


Fig. 4. Case 214. Osteogenic sarcoma in a man 37 years old. Amputation was done 1 year after the onset. The cortex is grossly well preserved and one is inclined to group it with subperiosteal tumors without a medullary involvement. However, tissue taken from the medullary cavity shows sarcomatous involvement.

unsafe because even if the average fair roentgenogram shows only an involvement of the periosteum or a subperiosteal tumor with an intact periosteum this is not conclusive. Frequently, when an unusually clear roentgenogram is made of the amputated extremity a more diffuse and extensive involvement can be made out than is seen in the routine examination. There is no satisfactory proof that such circumscribed osteogenic sarcomata really occur with an involved periosteum and intact subperiosteal tissue. Furthermore even if such conditions occur theoretically by the time they attract the attention of the patient they are more or less diffuse. Not only is it impossible to state the exact location of the tumor from the clinical and roentgenological examination, but, very frequently even with the gross specimen in hand it is hardly possible to say with certainty where the tumor invasion stops. Thus it is evident that no clear gross anatomical features distinguish the "periosteal" type from the "subperiosteal and medullary." Neither is the microscopic picture of the periosteal type entirely different from the subperiosteal and medullary. This contention is especially true when one excludes from the group of medullary sarcoma all tumors other than osteogenic. The frequent occurrence of various intercellular substances in the same tumor indicates that the disease is essentially one and the same, whether the bulk involvement is in the periosteum or extends more subperiosteally (Plate 1).

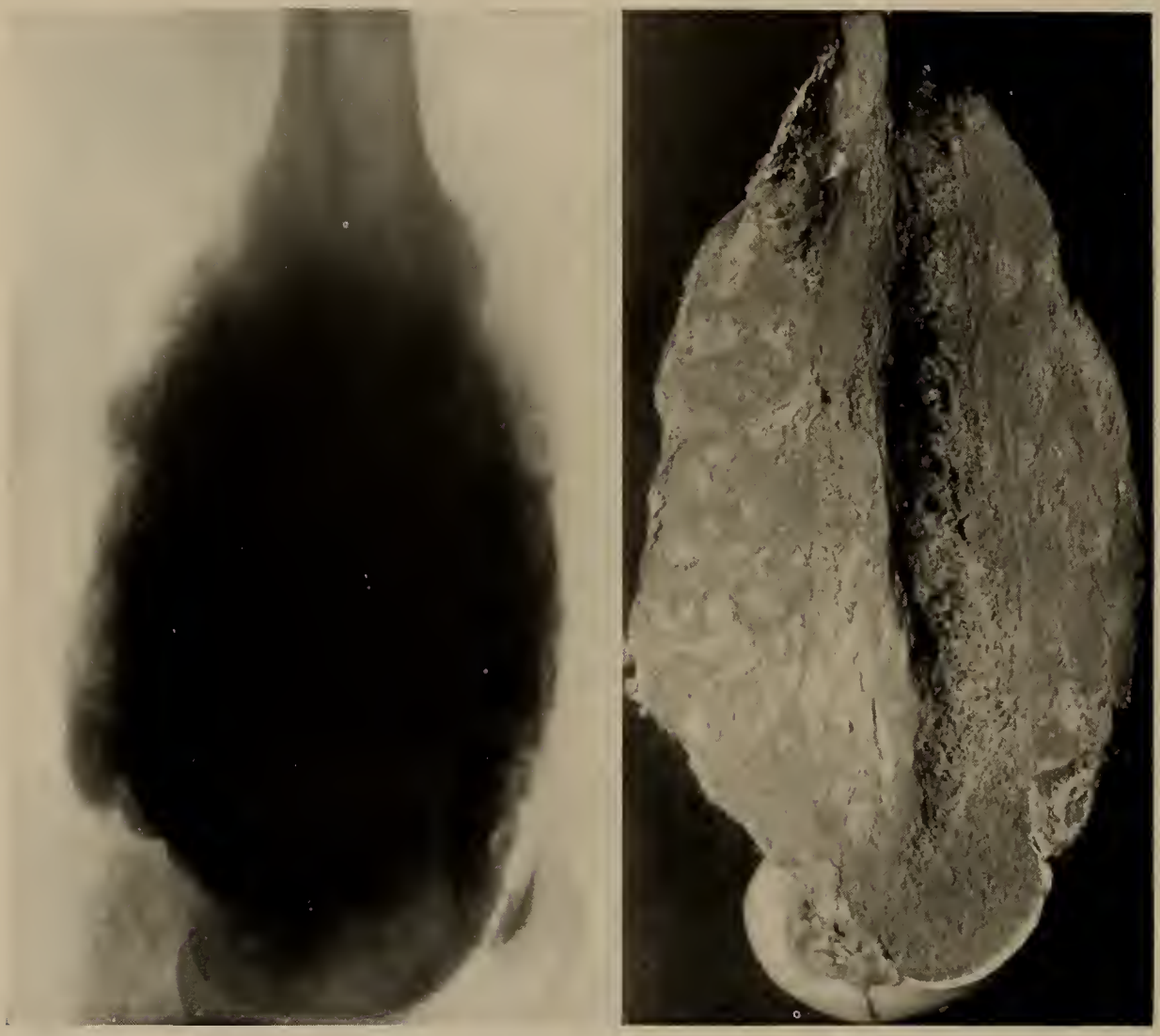


Plate 2. Case 116. See Figure 5. Osteogenic sarcoma in a woman 28 years old. The most outstanding sclerosing tumor in the roentgenogram in the Registry collection. The photograph of the tumor, however, indicates a soft vascular area in the proximal portion of the tumor, and in the medullary cavity. Death with pulmonary metastases 12 years after the onset. Amputation 6 years after the onset and reamputation for local recurrence 3 years later. The roentgenogram was taken 6 years after the onset.

Finally, it goes without saying that a most careful study of the material of the Registry did not furnish any evidence that the prognosis is different in a supposed periosteal osteogenic sarcoma from that of subperiosteal-medullary. In the Registry material if a satisfactory operative and pathological description is given or a good photograph of the gross specimen is present both periosteal and central involvement are seen (Fig. 4). Codman emphasizes this point.

Of all the four anatomical types of osteogenic sarcoma recognized by the Registry classification the "periosteal" has always enjoyed the greatest popularity. Some of the reasons of it have been pointed out above. Another reason is perhaps the fact that an involvement of the periosteum in the roentgenogram is one of the most widely recognized signs of osteogenic sarcoma. To the

Fig. 5. Case 116. Osteogenic sarcoma. The same tumor as in Plate 5. Sclerosing type of osteogenic sarcoma. In proximity to a sclerosing portion of the tumor a cellular area is seen.

inexperienced surgeon or roentgenologist few roentgenograms will suggest the diagnosis osteogenic sarcoma, unless there is the known fan-like structure or at least a lipping of the periosteum—the wedge-like lifting of the periosteum from the cortex of the involved bone. Lipping of the periosteum is a reactive response of the periosteum to bone involvement, and similar lipping is also met with in other than neoplastic bone lesions. However, good roentgenograms from various angles nearly always show it in osteogenic sarcoma and this means that subperiosteal involvement is present.

Investigators who have most consistently urged the recognition of periosteal sarcoma associated this type of bone involvement with the radiating fan-like structure of the tumor in the roentgenogram. It may be said without exaggeration that nothing in the teaching of malignant bone tumors is more popular than this fan-like picture. The idea that this picture is absolute proof of osteogenic sarcoma is widely spread and frequently a clinician will not make the diagnosis of osteogenic sarcoma unless this picture is seen. Facts speak to the contrary; a similar arrangement of the needle-like osteophytes perpendicular to the bone is sometimes found in low grade chronic bone infection, pyogenic or tuberculous.

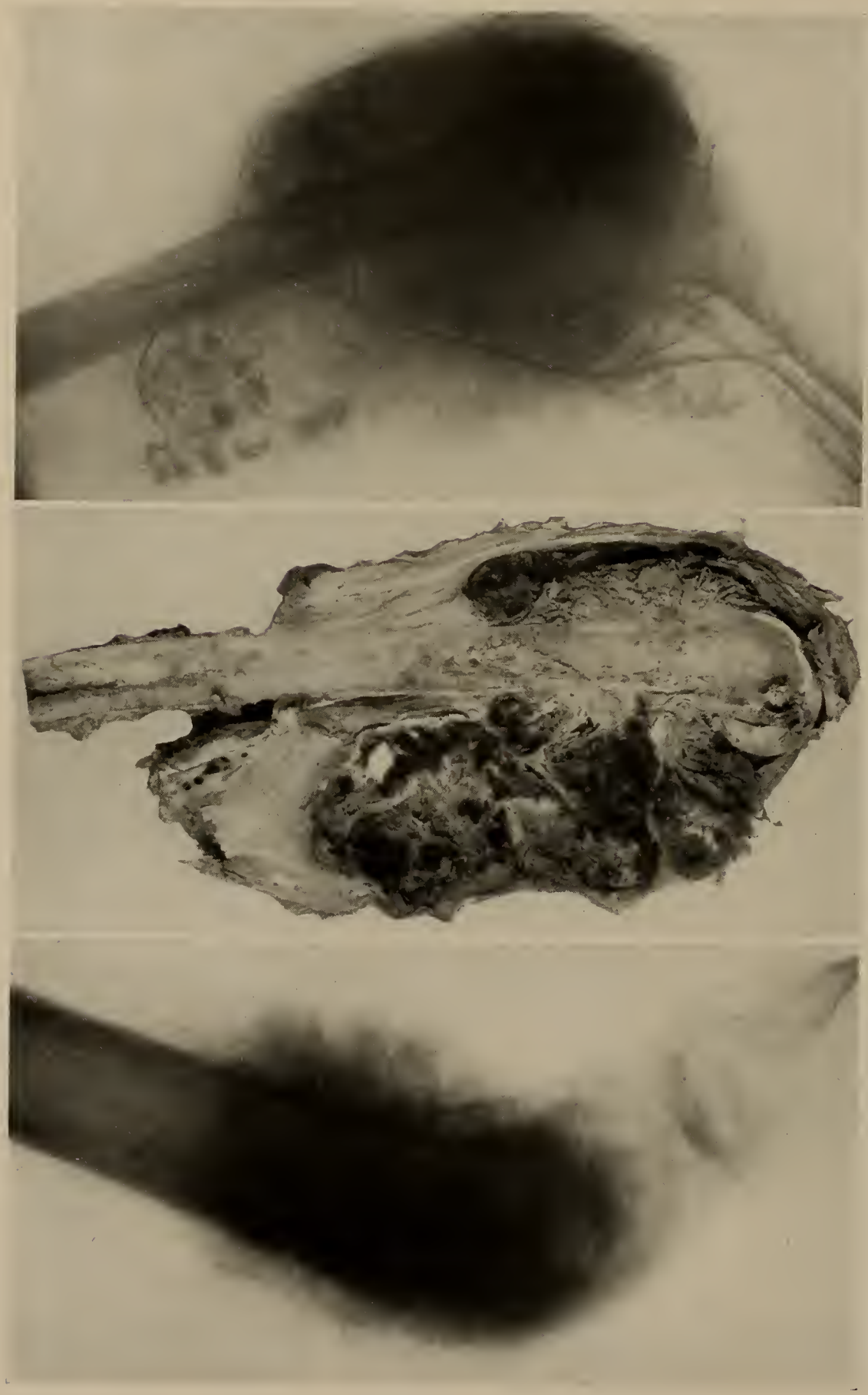


Plate 3. Case 334. Osteogenic sarcoma in a man 24 years old. The roentgenogram suggests a sclerosing tumor while the gross specimen and the specimen with the injected blood vessels show the exceptional vascularity of the tumor. The roentgenogram was taken 6 months after the onset and one month before a hip amputation was done. Death 10 months after the onset.

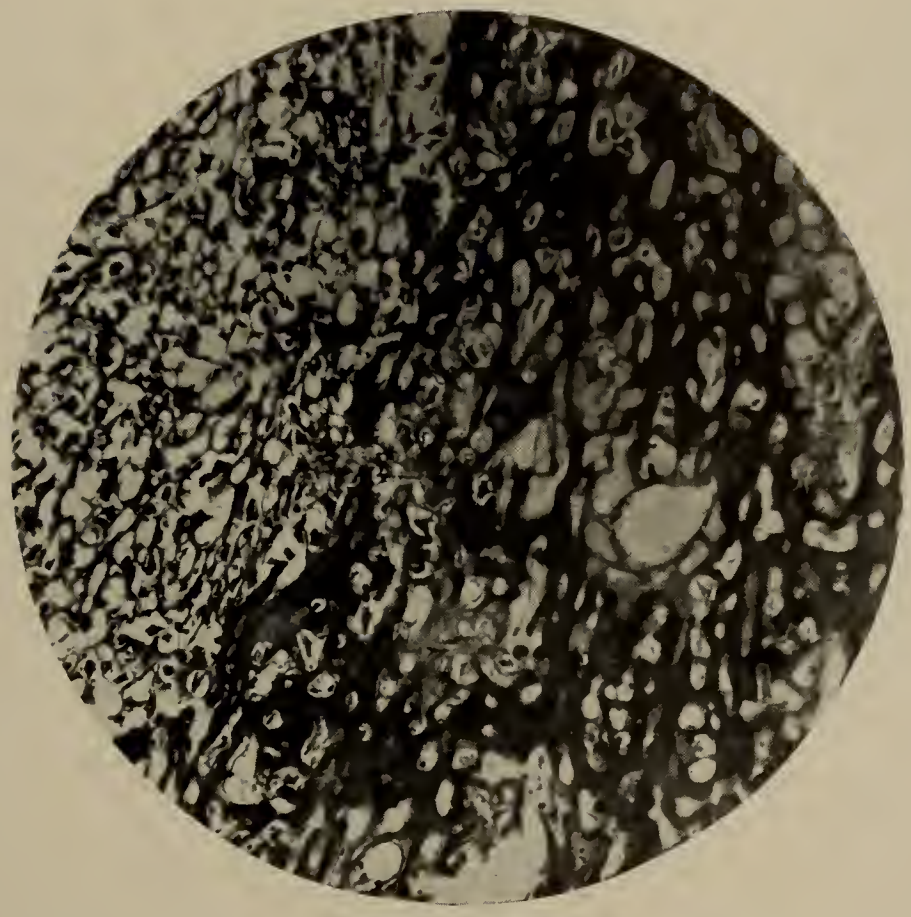


Fig. 6. Case 571. Osteogenic sarcoma. The same tumor as in Plate 1. Sclerosing type; close to the acellular tumor mass a cellular area is seen.

Beautiful specimens of macerated bones showing this condition may be seen in the Warren Museum in Boston and in the Army Medical Museum. The presence of these spicules means subperiosteal involvement, as will be seen later, but this is invariably accompanied also by a medullary involvement.

"Sclerosing" is the third anatomical type of osteogenic sarcoma in the Registry classification. The term sclerosing, given by Virchow, means that the tumor sclerosed, the intercellular substance ossified. In the Registry material and also in many cases of private collections studied I saw no case of osteogenic sarcoma in which the microscopic picture of "sclerosis" prevailed throughout the whole tumor (Plate 2). Usually after one or two areas of real sclerosed tumor where only an occasional tumor cell is found, areas are seen where the cellularity of the tumor and the pleomorphism of the tumor cells seem to indicate that no deviation from the grave prognosis of the average osteogenic sarcoma can be expected (Figs. 5, 6). Cases of osteogenic sarcoma studied roentgenologically during the whole natural life of the tumor frequently show at some stage or other, usually in the early beginning a picture simulating sclerosing osteogenic sarcoma (Plate 3). After weeks or months the character of the tumor changes to osteo-

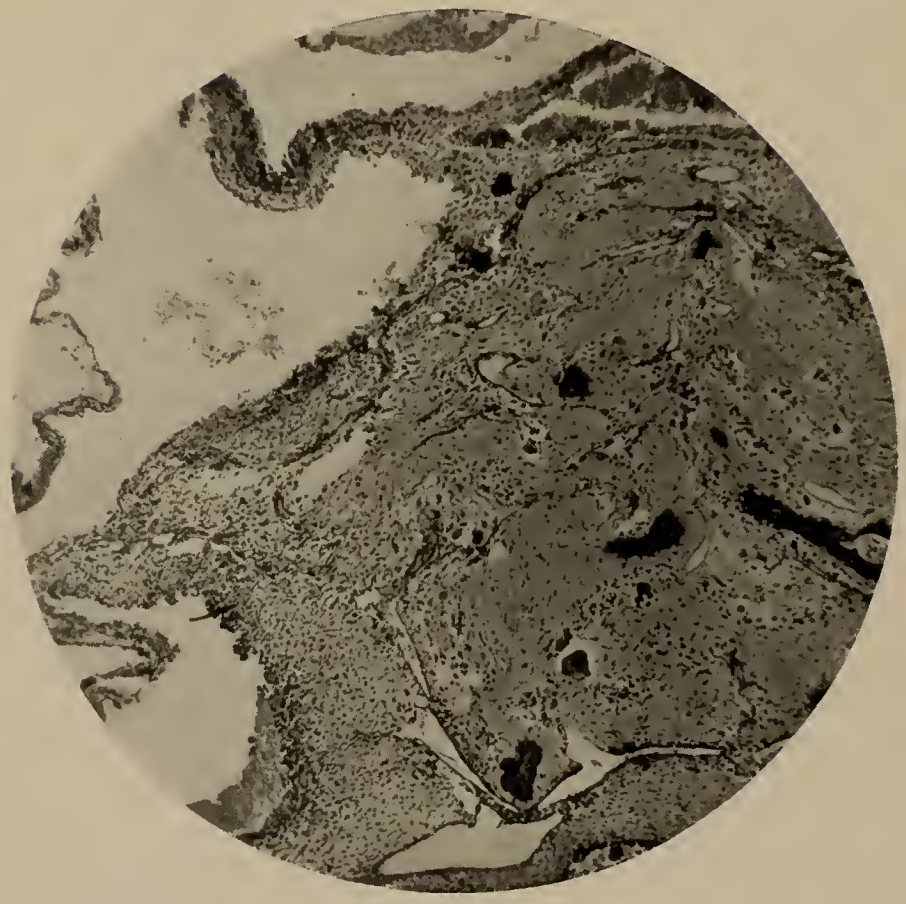


Fig. 7. Case 508. The same tumor as in Plate 18. An exceedingly vascular "telangiectatic" osteogenic sarcoma riddled with large blood spaces.

lytic. Were this tumor examined microscopically in its first osteoblastic stage one would be inclined to group it with the sclerosing tumors, while at a later stage the tumor would turn out to be definitely osteolytic.

The fourth anatomical entity of the Registry classification is the telangiectatic osteogenic sarcoma. As the meaning of the word suggests, this type is characterized by abundant blood vessels and spaces. In the extreme variety of this type when large blood vessels make up the main bulk of the tumor, and when only a thin wall of tumor tissue surrounds these blood spaces, a pulsation of the tumor may be felt (Fig. 7). In the old literature this variety of tumor was known as "bone aneurysm." The walls of the dilated blood channels being very thin and consisting of a single layer of endothelium, it is readily understood why a definitely poorer prognosis is to be expected in such cases; there is an immense opportunity for the malignant tumor cells to break into and to spread through the vascular system to the lungs. Like sclerosis in osteogenic sarcoma telangiectasis is a relative feature, all transitional stages being encountered between tumors with a poor blood supply and exceedingly vascular tumors. Telangiectatic is therefore also relative and not a definite separate type of osteogenic

sarcoma. It is obvious that telangiectatic is a postoperative or postmortem diagnosis; clinically and radiologically this diagnosis is usually impossible. Just as sclerosing is an extreme of differentiation of the tumor intercellular substance, telangiectatic is an extreme in the richness of the vascular supply of an osteogenic sarcoma.

Under heading 2 of the Registry classification is listed "periosteal fibrosarcoma." Under this term a sarcoma is understood which, though intimately related to the periosteum, leaves the cortex of the bone intact. Only very rarely the cortex of the bone is slightly eroded, the erosion taking place at a later date in the progress of the tumor. Thus, these tumors are extracortical, frequently surrounding the bone for a considerable distance. Virchow called attention to the fact that usually these tumors are found at points of bone insertion of tendons and dense fasciæ. The majority of these tumors present a typical dense fibrosarcoma. In the Registry material under "periosteal fibrosarcoma" are grouped also instances in which the origin of the tumor could not be established with certainty. A well ascertained true example of a sarcoma originating from the outer layer of the periosteum is up to the present day unknown in the Registry material. The "periosteal fibrosarcoma" cases registered however bear out the fact that this tumor is of a decidedly better prognosis than osteogenic sarcoma. It is easy to see that the term "periosteal fibrosarcoma," accepted by the Registry Committee, is unsatisfactory for important reasons. The word "periosteal" readily raises in one's mind associations with "periosteal osteogenic sarcoma," a tumor of an entirely different origin, microscopic structure, and mainly different clinical course. The Registry Committee seems to have realized it and has attempted to avoid confusion by adding the word "fibrosarcoma" to "periosteal." V. Rindfleisch has pointed out that the origin of "periosteal fibrosarcoma" is from the "fascicular" layer of the periosteum, while the "periosteal osteogenic sarcoma" originates from the cambial layer. In the literature two other terms are mentioned for this tumor: "parosteal" and "extraperiosteal." Of these two I prefer the latter. "Parosteal" conveys rather an idea of a process spreading along lines parallel to the bone; parosteal sarcoma is a sarcoma of a fascia or muscle rather than of the periosteum itself, while "extraperiosteal" seems to emphasize the origin of the tumor from the "external" fascicular layer of the periosteum.

The sixth division of the Registry classification is "angioma." Two subheadings are given there: the benign angioma and the malignant. Of the second subdivision, the malignant, which alone is to be considered here, no cases are registered with the Committee. The Registrar, Codman, believes that this type, angiosarcoma as he calls it, is exceedingly rare if it exists at all; most angiosarcomata from the literature he regards as telangiectatic osteogenic sarcomata. It is true that much confusion was aroused in our knowledge of tumors

of the vascular system by the term "angiosarcoma." This term, given by Kolaczek, originally was intended for the so-called peritheliomata, tumors originating from the vessel wall and not from the endothelial lining of the vessel. Later this term found its way to tumors with a clear endothelial origin, which are better called angio-endothelioma. Unfortunately the very lax requirements instituted by Golgi and Kolaczek for a diagnosis of an endothelioma have led to frequent diagnoses of endothelioma in cases in which no such condition was present. This fact greatly discredited the angio-endotheliomata as an actual anatomical entity in the eyes of most leading pathologists. The majority of pathologists are unwilling today to diagnose an angio-endothelioma even when all evidence is before them. Because of this skepticism instances of true angio-endothelioma slip by under various other diagnoses. This is also true of angio-endothelioma of bone. During the study of the Registry material I found two cases of primary angio-endothelioma of bone which had been passed by the majority of examiners as metastatic tumors. Angio-endothelioma of bone is a malignant tumor of the vascular system of bone with a typical microscopic structure and a definite origin from the endothelial lining of the vessel wall.

I realize that the rarity of skeletal angio-endothelioma would not justify a segregation of this condition as a separate clinical entity in a classification of practical clinical importance. In a large series of malignant bone tumors a careful study will occasionally mark instances which will be difficult to classify according to their anatomical structure and clinical behavior. Obviously such instances cannot be all brought out as clinical entities if the classification of such an obscure condition as bone sarcoma is to remain clear and digestible. Such instances must be pigeonholed awaiting accumulation of more accurate knowledge of bone tumors in general. To such a group of "unclassified tumors" it would be well to carry the angio-endothelioma of bone which although a clear anatomical entity is too rare to justify a separate heading in the classification. It is probably best to list under this group also the extraperiosteal sarcoma (periosteal fibrosarcoma of the Registry classification), true representatives of which seem to be very rare. To this group should belong also such questionable cases as No. 420 and No. 349 of the Registry collection, the first a tumor resembling somewhat a giant cell tumor in the primary and pulmonary metastases but not typical enough of a true giant cell tumor structure, and the latter a true giant cell tumor which, following multiple operations and ill advised therapeutic procedures, was transformed into a distinct malignant tumor and gave pulmonary metastases.

The seventh division of the Registry classification is "Ewing's tumor." The knowledge of this entity, scarce as it is, is unfortunately limited only to those who have studied the Registry material. This fact however is not surprising when one recalls that only in 1920 was this tumor established by Ewing as an anatomical and clinical entity among the malignant bone tumors. Pathologists

unfamiliar with bone tumors have been for long submerging and still continue to submerge Ewing's tumor under the diagnosis of round cell sarcoma or solitary myeloma. A specific clinical course, a typical gross anatomy, and a unique histology serve as the basis for the existence of this entity. In studying the Registry material even without any thought of classifying the tumors it is surprising with what ease the impression grows in one's mind that these tumors represent a clear-cut separate disease. This tumor affects young patients, rarely above 21 years of age. It frequently begins with a clinical picture resembling acute osteomyelitis, a reason why in the majority of cases this mistake in diagnosis is usually made. The response of the tumor to radiation, whether roentgen-ray or radium is remarkable; however, permanent cure from radiation is as yet unknown. Metastases to other bones is a characteristic feature of the terminal stage of this tumor in divergence with osteogenic sarcoma in which bone metastases are very infrequent. The histological structure of the tumor is at variance with any variety of osteogenic sarcoma. Ewing suggests the origin of the tumor from the endothelium of the bone marrow. In connection with this he suggests a wider scope of cellular elements for the term "endothelium," since he admits that the vascular endothelium bears no relation to the origin of the tumor. Deferring for the present time a detailed discussion of this question it will suffice to say that no proof has as yet been accumulated to support Ewing's hypothesis of the endothelial origin of this tumor. The term "endothelioma" under which this tumor frequently appears tends to confuse it in the minds of the occasional observer with angio-endothelioma. If Ewing's tumor is in any way related to the endothelium of the bone marrow it is an "endothelial myeloma" and it should not be called "endothelioma." It is most satisfying to see that the Registry classification has refrained from either term, endothelioma or endothelial myeloma. However the term Ewing's tumor decided upon by the Registry Committee is not well chosen and is incompatible with the intention of the Registry to reserve the word "tumor" for a giant cell sarcoma which is essentially benign. In giant cell sarcoma the word sarcoma has been replaced by the word tumor in order to emphasize the benign nature of the lesion. The lesion understood by the Registry Committee under Ewing's tumor is a true malignant condition and the retaining of the word sarcoma would cause less confusion as to the clinical behavior of the tumor. For this reason I am of the opinion that Ewing's tumor should be substituted by Ewing's sarcoma until a time when we learn more of the nature of this condition, more of its origin and its morphological ancestry. For the present, whatever the morphological nature and the origin of this tumor, it is undoubtedly a clinical entity and as such it is entitled to an independent place in the classification.

"Myeloma" occupies the eighth division in the Registry classification. This is a tumor originating in the medullary cavity of a bone, appearing simultaneously

as numerous nodules ranging in size between the size of a pin head and that of a walnut. The large majority of myelomata are multiple tumors, only one solitary tumor having been recorded by the Registry during the six years of its existence. This tumor is held to be derived from the specific bone marrow cells of the myelocyte series. Myeloma is the only true round cell tumor occurring in bone. Because of its multiple character myeloma was recognized long ago as a systemic disease, and this recognition led to a view that myeloma is not a true tumor but is to be regarded as in some relation to the pseudoleukæmic or aleukæmic group. For purposes of classification there is no need to enter a discussion of all the fine details of the derivation or etiology of myeloma. There are characteristic features which stamp myeloma as different from osteogenic sarcoma. Myeloma is a bone marrow tumor characterized by multiple foci of origin, by frequent albumosuria and rare metastases, frequently affecting short bones, and especially favoring the ribs, sternum, vertebræ, and skull. When situated in long pipe bones, it favors midportions rather than the ends of the bones. Myeloma recedes rapidly under radiation but no permanent recovery by radiation is recorded. In many of these features myeloma resembles Ewing's sarcoma, from which it is easily distinguished because of its morphology and different radiological appearance. The wide destruction of the bone marrow leads to early cachexia and anæmia, and because of the rapid resorption of bone, fractures and infractions occur early and frequently. Attempts at subdivision of myeloma into separate types according to a variation in morphology has met with much opposition. The present day knowledge of the fine points of morphology of myeloma is limited. Subdivisions according to histological features offer no therapeutic indications. Despite the divergence in the histological structure all these types belong essentially to the same disease entity.

As a conclusion to the above discussion all primary malignant bone tumors can be subdivided in the following groups:

1. Osteogenic sarcoma.
2. Ewing's sarcoma.
3. Myeloma.
4. A group of unclassified sarcoma including among others such "near entities" as angio-endothelioma and extraperiosteal sarcoma.

No subdivisions of the main groups in types is recommended. Slight as are these changes of the Registry classification insofar as sacrifice of accurate knowledge for the sake of simplicity is concerned, they are important because of the clearness with which they present the classification of this most confused chapter of oncology. That these changes are justified theoretically was pointed out in the analysis of the Registry classification. From the practical point of view there can be no doubt that these changes render the classification of the primary malignant bone tumors more understandable for the roentgenologist and patholo-

gist and especially for the clinician, who is ordinarily relatively inexperienced in bone tumors.

This modification of the Registry classification is not to be considered as wholly satisfactory and final. No clear cut or hard and fast rules are possible in dealing with such a confused problem as malignant tumors of bone. There is no assumption on my part that in the future with the advance of our knowledge of these tumors it will not be found advisable to subdivide these four entities into groups and types with a peculiar histology, origin, and clinical picture. When a classification of a group of pathological conditions, as in bone tumors, precedes the acquisition of exact knowledge of these conditions the only way a classification can proceed is the deductive one, by dividing the general group into narrower and more specific classes. This explains why sometimes bone tumors are encountered when it is difficult to include them in any of the divisions of the classification. In the present classification these tumors are grouped under the "unclassified." The number of individual cases in this group is not large and with the advance of our knowledge will decrease still more. Occasionally the question will arise whether to group them with one or the other division. These are the so-called borderline cases, which, with all clinical and radiological data and the gross specimen before him, and with the section under the microscope, one hesitates to place in any certain group. The question of the decision of the exact nature of a borderline case is especially difficult when the diagnosis rests between a malignant tumor with a very grave prognosis and a benign condition, whether a tumor growth or an inflammatory process. In these cases the pathologist's answer is most decisive and therefore most responsible as far as the therapeutic and especially prognostic indications are concerned. *Natura non facit saltum* and there may be expected all transitional stages from a benign condition to the most fatal tumor growth. No classification can with advantage consider similar problems as long as our knowledge of bone tumors is so meager, and our experience so fallacious. However, at present I agree with Codman that any pathologist who has studied the Registry material with care will make a satisfactory diagnosis and prognosis in over 90 per cent of the cases presented to him, provided the data are technically good.

OSTEOGENIC SARCOMA

Pathology—*Gross Anatomy*

THE pathology of primary malignant tumors of bone embraces the gross anatomical picture of the tumors and their histological structure. Unlike other pathological conditions the gross anatomy of these tumors is more complicated because of their location in such a dense unyielding organ as bone. Because of the great resistance to the spread of the tumor offered by the bone and also because expansion of the bone alone is far insufficient for a progressive growth of the tumor, the gross picture of these tumors is exceedingly peculiar. This is especially true of osteogenic sarcoma—that main group of primary malignant tumors of bone.

As was pointed out in the chapter on classification a distinction between central, subperiosteal, and periosteal osteogenic sarcoma is unfounded. An osteogenic sarcoma is a diffuse process of the involved bone and there is no way to determine precisely the origin of the tumor, i.e., whether medullary or periosteal. Of course there is always a period in the history of an osteogenic sarcoma when the most active growth of the tumor is especially pronounced in one certain area of the involved bone, whether it be the medulla, cortex, or periosteum. It is evident that the gross picture will be influenced as to whether the tumor grows more rapidly in the region of the medullary cavity or close to the periosteum. In the first case the bone cortex will exercise resistance to the spreading of the tumor for a much longer period of time than in the last case, when the periosteum will be reached and perforated by the tumor at a much earlier date. It is evident therefore how erroneous it is to accept as the origin of the tumor the center of the tumor mass, which in many cases even late in the disease is confined by the cortex although the latter may be perforated in many places.

To understand the capricious features characteristic of osteogenic sarcoma one has to keep in mind the main factors which influence the gross picture, shape, and consistency of these tumors. The foremost place among these factors is occupied, on one hand, by the continuous aggression of the tumor elements and on the other by the defensive protective measures of the involved bone against the growing tumor. The degree of differentiation of the tumor elements, the vascularity of the tumor and the regressive changes in it are factors greatly influencing the consistency of the tumor.

The aggression of the tumor cells and the defense of the involved bone may be noticed in every case of osteogenic sarcoma. The natural instinct of the tumor—to grow and to increase in size—leads to more or less destruction of the bone in the involved area. Destruction of the bone to a greater or lesser degree is a condition *sine qua* there is no osteogenic sarcoma. The attempts of the tumor to extend are directed in two ways—one is toward the outer aspect of the bone and the other is along the medullary cavity. This latter direction is a point of less resistance, because of the loose structure of the bone-marrow and also because the endosteum does not exercise as much activity to protect the medullary cavity from invasion of the tumor as the periosteum does against perforation of the cortex into the surrounding tissues. This explains the fact that cases of osteogenic sarcoma are seen in which the medullary cavity is literally stuffed with tumor from end to end while the radiograph indicates a tumor wholly limited to the area of involvement of the cortex and periosteal reaction.

The self defense of the involved bone is taken over by the periosteum. The periosteal reaction in osteogenic sarcoma is the only morphologically evidenced attempt of the organism to protect itself against this extremely malignant condition. The periosteal reaction is especially well expressed when the tumor is located in its most frequent situation—the metaphysis of a long pipe bone. It is much less striking when the tumor is located in the shaft or in those rare cases when it is situated in the epiphysis proper. The periosteal reaction of a bone involved with an osteogenic sarcoma consists in formation of new bone, apposed on the outer surface of the cortex of the involved bone. This apposition of new bone leads to a gradual thickening of the bone. Gradually the tumor breaks its way through the old cortex by way of the Haversian system and encroaches upon the newly apposed periosteal bone which it gradually displaces. Slowly the tumor spreads subperiosteally along the surface of the bone. The periosteum is being pushed away from the underlying bone by the newly produced protective osseous tissue and especially by the growing tumor mass. Nothing interferes with this elevation of the periosteum except the defensive lipping to be described later until the stripping off of the periosteum reaches the epiphyseal line. Because of the most intimate attachment of the periosteum to the epiphyseal cartilage here the elevation of the periosteum comes to a stop and further growth of the tumor leads to a club shaped enlargement of the epiphyseal end of the spindle. It is of sufficient diagnostic importance to remember that in osteogenic sarcoma the old cortex is frequently seen passing through the tumor mass appearing grossly intact. Permeation rather than perforation of the cortex expresses better the pathological process. In this, osteogenic differs from Ewing's sarcoma, in which the bone generally is broken up and displaced by the tumor.

The gross structure of the tumor mass consists of stalactite-like rods of hyaline osteoid and osseous tissue arranged like the spikes of a wheel perpendicular to

the long axis of the involved bone or like fluffy trabeculæ spread beneath the periosteum on top of the cortex of the involved portion of the bone. In the radiograph the first structure is represented by the classical sun-ray-like appearance.

Not infrequently the periosteal reaction is expressed in only slight bone production. This is common in osteogenic sarcoma of the shaft. The rapidly enlarging tumor leads to an elevation of the periosteum from the involved bone in the manner outlined above, but the periosteum is unsuccessful in forming a true bony capsule about the tumor. Only at the polar ends of the grossly fusiform swelling which are farthest from the most active portion of the tumor, the periosteally new formed bone has temporarily escaped destruction. In the radiograph this new formed bone with a jagged edge gives the picture of "lipping," which is a cardinal sign of osteogenic sarcoma not yet sufficiently appreciated (Plate 4). Physiologically this lipping is a result of stretching of the periosteum by a mass intruding between the bone and its periosteum. In a periosteum put under tension the osteogenic capacity is greatly stimulated. Hence such a lipping is sometimes encountered in merely traumatic conditions when a hæmorrhage strips away the periosteum from the bone. Thus, while lipping is a sign of malignancy, it is not in itself a result of malignant tissue. In the extremely rapidly growing osteogenic sarcoma lipping is less distinct, the lips are poorly formed because of a lack of time for their formation and also because of the extremely intense bone destruction.

In cases with a rapid growth of osteogenic sarcoma and a weak periosteal reaction pathological fractures are encountered. Such fractures at once give an outlet to the expanding tumor by tearing the periosteal capsule. The tumor then enters the ultimate phase in its local development, infiltration of the surrounding soft tissue. More frequently, however, than through a pathological fracture, an osteogenic sarcoma reaches this final stage by way of perforation of the periosteal capsule. The continuous stretching of the periosteum by the tumor expanding beneath it finally leads to a perforation of the periosteum at some point. The tumor changes its main direction of expansion along the bone to a centrifugal infiltration of the surrounding tissue. A longitudinal section through a tumor at this stage shows the involved bone with the tumor mass spreading along it, intramedullary and subperiosteally, and externally to the periosteum, the most recent tumor mass connected with the main tumor by a pedicle through the perforation. In perforation through the periosteum of osteoblastic osteogenic sarcoma, when the subperiosteal portion of the tumor consists of the stalactite strands of hyaline osteoid and osseous tissue, the extraperiosteal portion of the tumor loses this radiation structure and the osteoid and osseous tissue of the tumor here has no evident orderly arrangement.

After perforation of the periosteal capsule has taken place, nothing more stands in the way of the aggressive tumor. Muscles are stretched, thinned, and

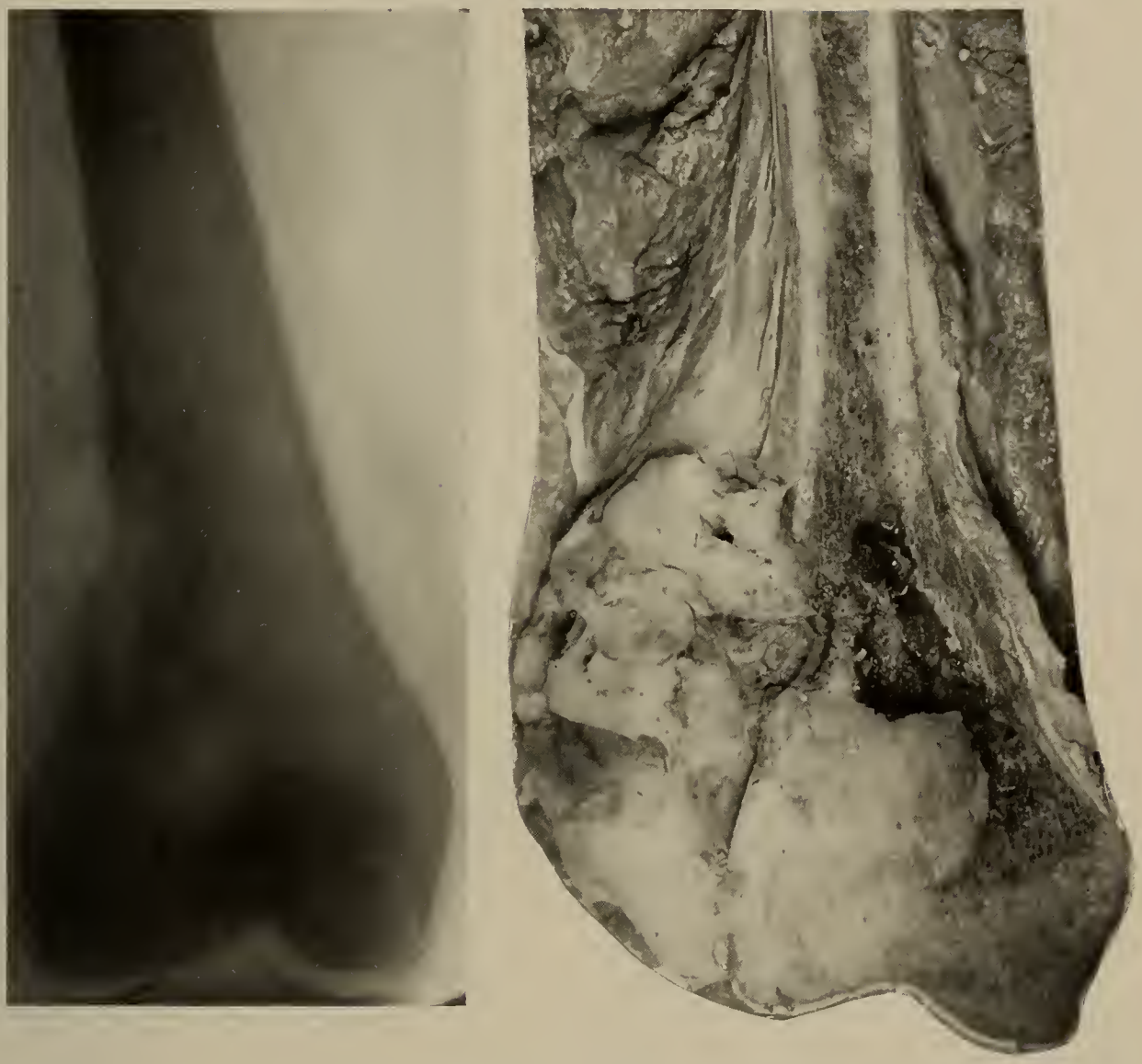


Plate 4. Case 43. Osteogenic sarcoma in a girl 17 years old. Osteolytic variety. The photograph shows invasion of the epiphysis and lipping of the periosteum.

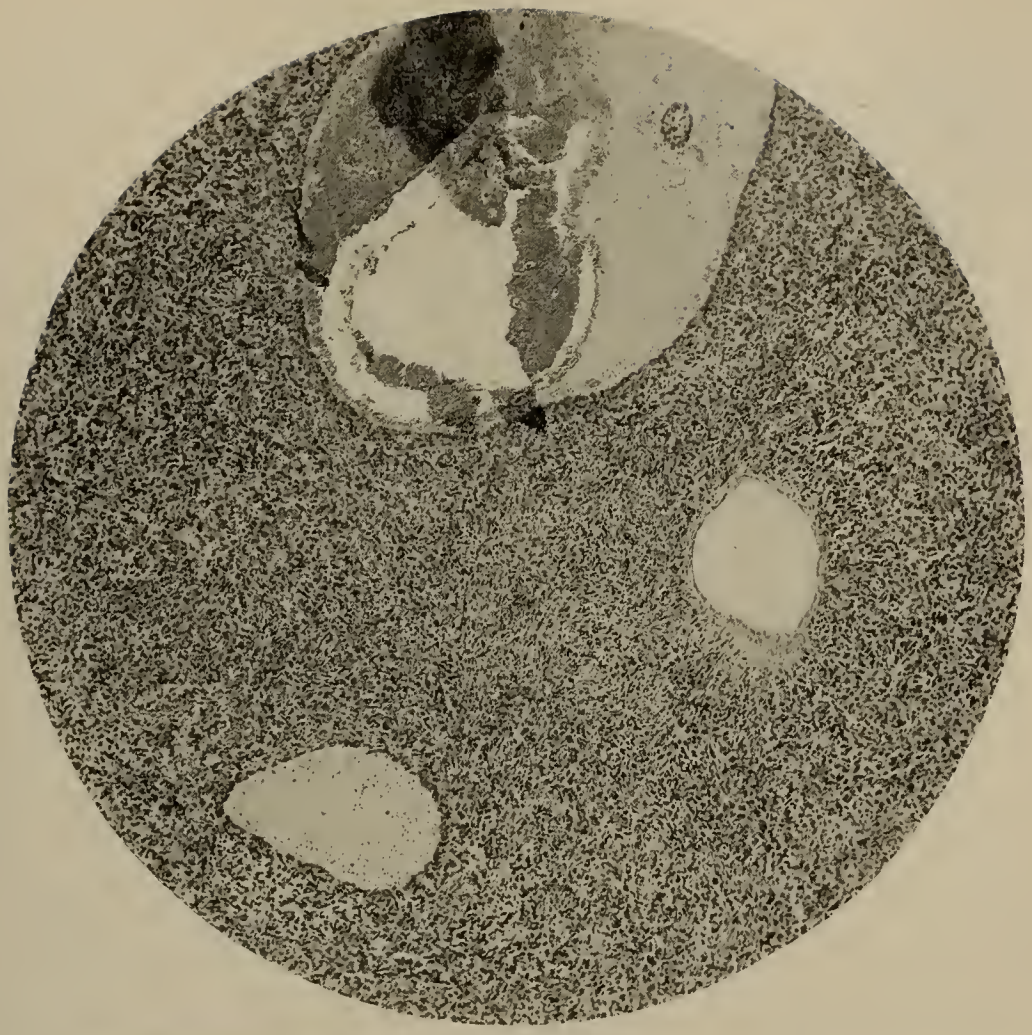
atrophied so that it is not unusual to find the tumor covered merely with glossy skin. Ulceration of the overlying thinned out skin is unknown in osteogenic sarcoma; it is simply stretched and atrophied. Even more resistant to osteogenic sarcoma than skin is cartilage. Articular cartilage and cartilage of the epiphyseal junction offer more resistance to the aggressive tumor than any other tissue in the human body (Fig. 8). The best explanation of it is probably the absence of vascular channels in cartilage. As a matter of fact in adults with ossification of the epiphyseal line an involvement of the epiphysis by an osteogenic sarcoma of the metaphysis takes place relatively early, while in young individuals an extension involvement of the epiphysis is more likely to take place by the indirect route of perforation of the metaphyseal periosteum and secondary involvement of the epiphysis from without than by direct extension through the car-

Fig. 8. Case 498. Osteogenic sarcoma. Illustrating the resistance of the articular cartilage to the tumor invasion. A layer of spongiosa is seen between the tumor mass and the articular cartilage.

tilaginous epiphyseal line. In approaching the articular cartilage the tumor destroys all the bone, leaving a thin layer of spongiosa which separates the cartilage from the tumor mass. In this respect osteogenic sarcoma differs from giant cell tumor where the cartilage is frequently in direct contact with the tumor. However instances are known when the entire articular cartilage *en masse* was found separated from the underlying bone destroyed by the tumor which was infiltrating the joint cavity.

Perforation of an osteogenic sarcoma into the joint with an actual involvement of the articular synovia is not rare in far advanced cases complicated with a pathological fracture or by surgery in a region close to the joint. More unusual is a spontaneous involvement of a joint without a preceding pathologic fracture. After perforation into the joint cavity the tumor grows freely and a subsequent involvement of an adjoining normal bone is known to occur.

It is easy to see that an exploratory incision or incomplete local excision of an osteogenic sarcoma readily changes the entire course of the disease. The perforation of the periosteal capsule, long awaited by the tumor, is brought about in these cases by the surgeon himself. Articular involvement in similar cases is not infrequent.



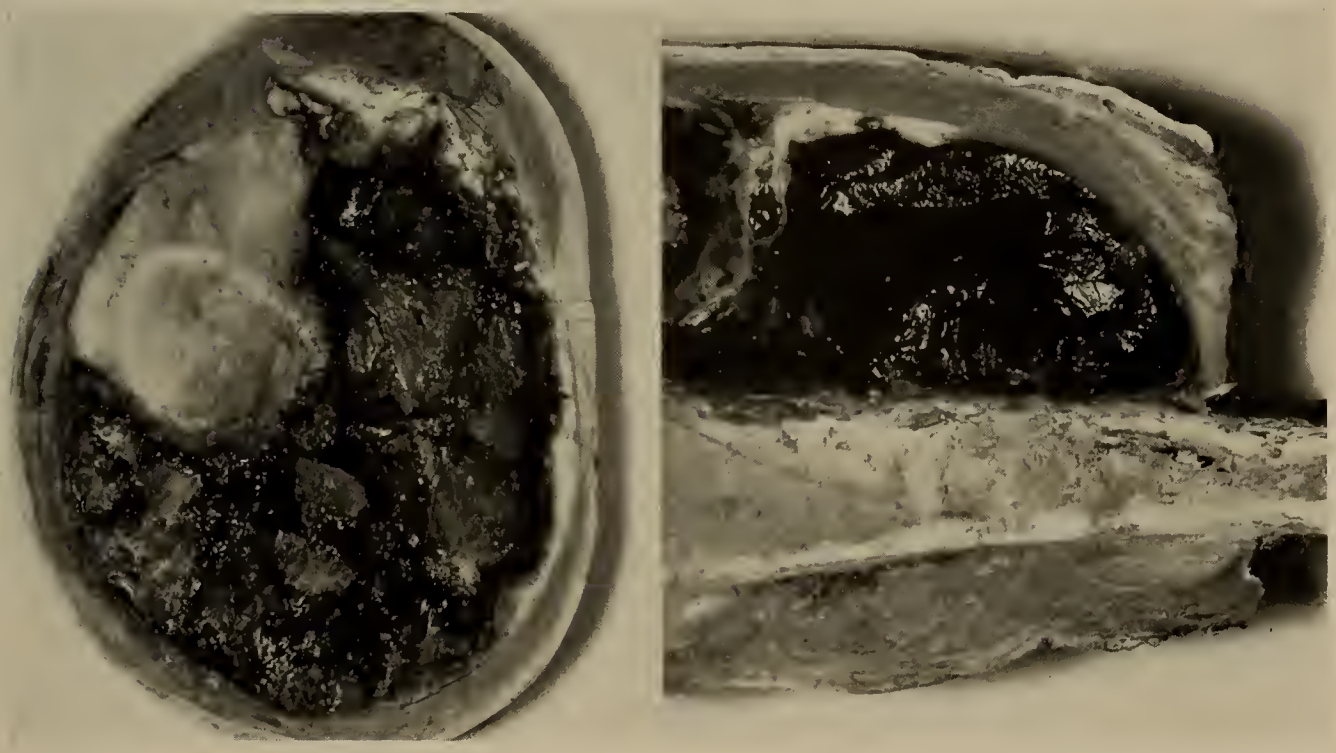


Plate 5. Case 98. See Figure 28. Pulsating osteogenic sarcoma; "malignant bone aneurysm" of the old authors.

Fig. 9. Case 623. Osteogenic sarcoma. Showing the structure of the so-called medullary fibrosarcoma; an osteolytic variety of osteogenic sarcoma.

The consistency of an individual osteogenic sarcoma is influenced chiefly by the degree of differentiation of the elements constituting the tumor. The great variety in consistency an osteogenic sarcoma may attain is best understood if one thinks of all the changes in consistency which may be presented by immature callus in which the differentiation was interrupted at some stage of development. There are all the transitional stages from the very first attempts of organization of the blood clot between the bone ends through the stage of fibrosis and cartilage formation up to consolidated bony callus. Our knowledge of the morphology of bone repair and regeneration is too meager to enlighten us on the origin and the various stages of the development of an osteoblast. There is, however, considerable evidence tending to show that fibrous tissue, myxomatous tissue, and cartilage are definite stages through which osseous tissue may pass during its development. These definite stages are met in osteogenic sarcoma. In some, the differentiation of the tumor elements goes on to formation of fibroblasts, in others it is sidetracked to myxomatous tissue, in still others the ability of the cells to differentiate goes no further than the stage of cartilage, while in some osseous tissue is formed. The consistency of osteogenic sarcoma, however, is not

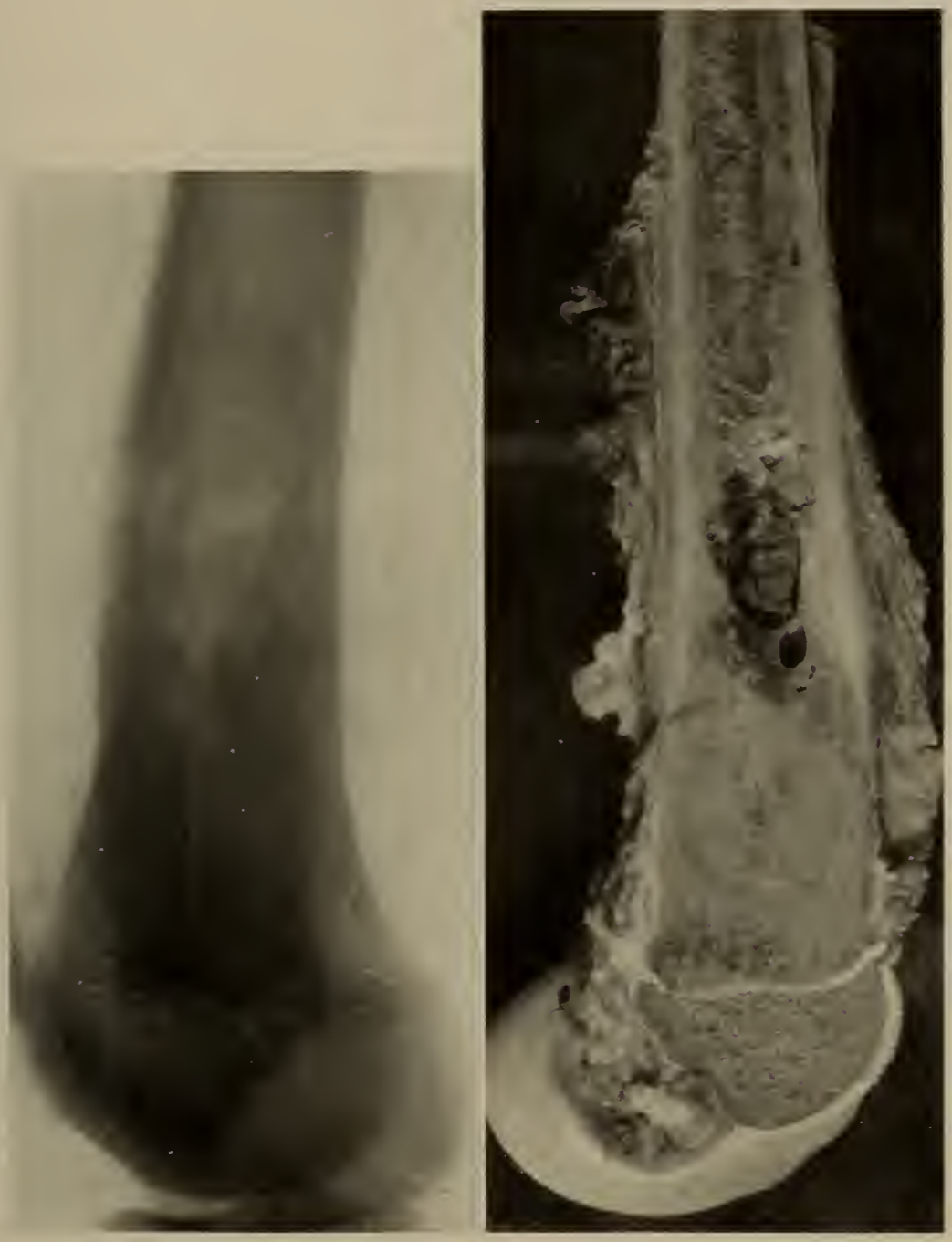


Plate 6. Case 341. Osteogenic sarcoma in a boy 15 years old. Notice the cyst in the gross specimen; a result of central degeneration of the tumor. Death 1 year and 10 months after the onset.

defined by the presence of one certain type of tissue—in the majority of cases usually two or more various tissues may be observed simultaneously.

According to the degree of differentiation of osteogenic sarcoma these tumors are usually divided in two groups: osteoblastic and osteolytic depending upon the degree of bone production or destruction. From the material studied I believe that there are no pure osteoblastic or pure osteolytic osteogenic sarcomata. The tendency of all cases of this class of sarcoma is to produce bone in

Fig. 10. Case 584. Osteogenic sarcoma in a girl 19 years old. Amputation was done after heavy radiation therapy. Notice the extensive cyst; the cyst was filled largely with necrotic tumor tissue.

some part of the tumor, because, as it was pointed out above, the cells of which an osteogenic sarcoma is composed are of the osteogenic variety. An osteolytic tumor, having destroyed much of the involved bone, usually shows minute foci of new formed bone sparsely scattered through the tumor, which when the tumor is cut give a gritty sensation. In an osteoblastic tumor we see along with masses of new formed bone, casting the characteristic dense shadow in the roentgenogram, also numerous minute foci of cellular areas without any trace of bone formation. There is, however, a decided difference in the consistency of an osteoblastic and osteolytic osteogenic sarcoma. The softness of an osteolytic osteogenic sarcoma ranges between the firm elastic consistency of cartilage and the semifluid consistency of myxomatous tissue. Besides minute foci of bone,

Fig. 11. Case 313. Skeletal chondroma. The tumor is incised and the central portion laid open. Showing extensive degeneration with cyst formation in the cartilaginous matrix.

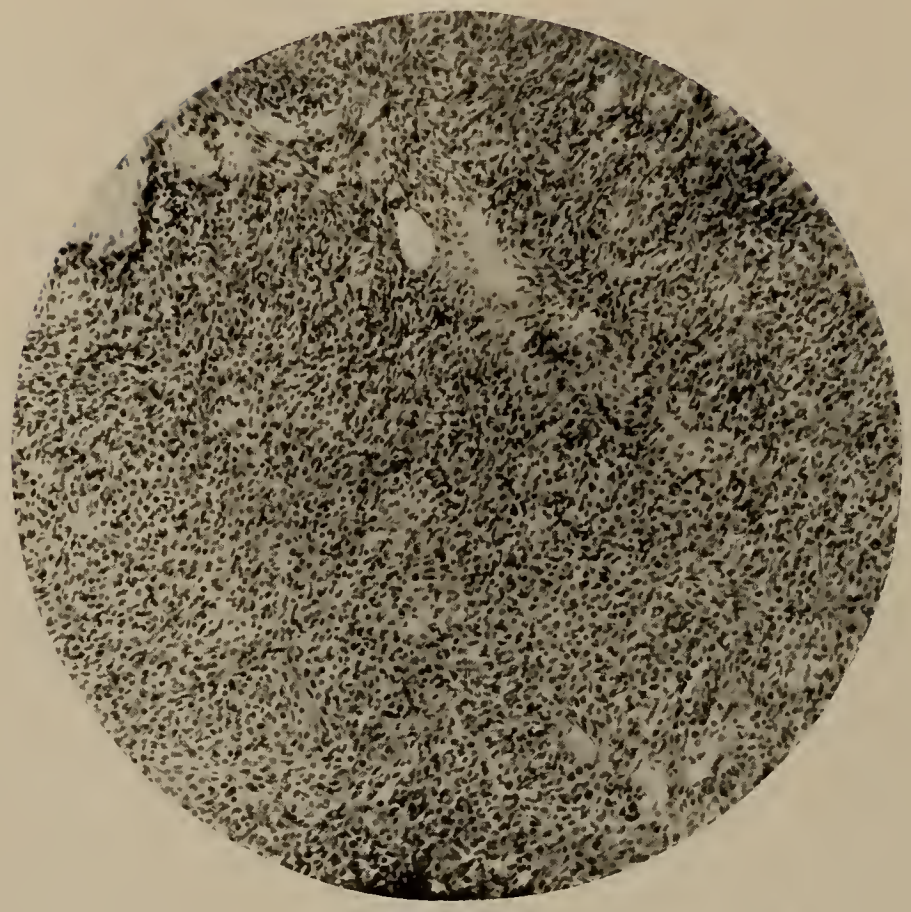


Fig. 12. Case 462. Small spindle cell variety of osteogenic sarcoma.

osteolytic tumors are composed of cartilage, myxomatous tissue or fibrous tissue, or a combination of two or all three. The consistency is dependent upon the prevalence in the tumor of any one of these tissues.

From the standpoint of the theory of "repair and growth restraint" osteolytic osteogenic sarcomata may be regarded as tumors in which the differentiation of the cellular elements has proceeded to a certain point on the long path between the primitive mesoblast and the mature osteoblast. In relation to this two observations are interesting. One is that osteolytic tumors are much more frequent in adults than in children and adolescents; and the other is that an osteolytic osteogenic sarcoma more frequently invades the epiphysis than an osteoblastic osteogenic sarcoma. The latter fact is probably merely a result of the former—the ossified epiphyseal line in adults is not resisting to an epiphyseal invasion of a metaphyseal osteogenic sarcoma. The fact that osteolytic osteogenic sarcomata are met more frequently in adults in whom the regenerative powers of the bone are weaker than in the young seems to correspond well with the expressed idea of an osteolytic tumor being an undifferentiated osteogenic sarcoma.

The consistency of an osteogenic sarcoma with the preponderance of fibrous tissue is not very different from that of a fibroma, especially of the sclerosed

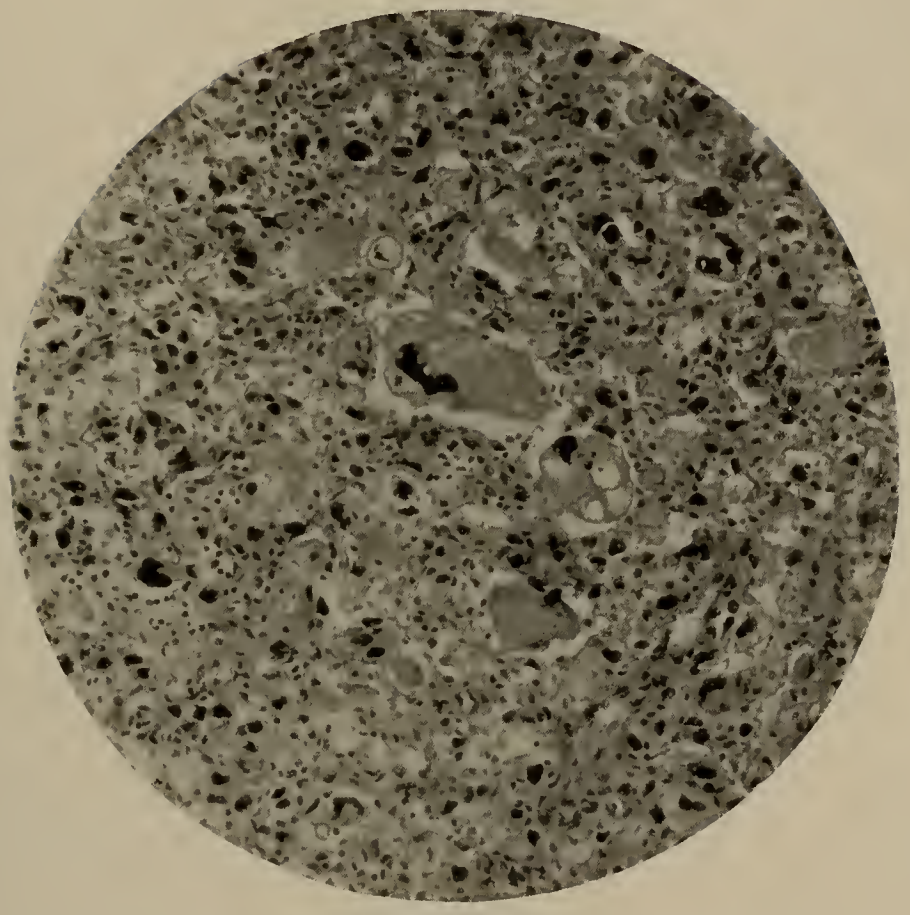


Fig. 13. Case 540. Osteogenic sarcoma. Showing the large polyhedral cells, said to be undifferentiated cartilage cells.

variety. An extensive destruction of bone with a substitution of a large fibroma is extremely rare, only two cases having been recorded in the Registry. Osteolytic tumors with prevalence of fibrous tissue are frequently located close to the medulla and this fact has been brought (Phemister) as evidence of the necessity of the recognition of "medullary fibrosarcoma" as a separate anatomical entity. The constant findings in such tumors of traces of bone formation, however, seem to contradict the rationality of a separation of these tumors from the group of osteogenic sarcoma. The clinical course and ultimate results furnish hardly any evidence of the exclusiveness of this variety of osteogenic sarcoma. Histologically a medullary fibrosarcoma is an exaggerated osteitis fibrosa in which the development of fibrous tissue is so extensive that it leads to an atrophy of the cancellous bone (Fig. 9).

When cartilage prevails in the osteolytic form, the tissue is firm, elastic, gritty, with the grayish white, semitranslucent, milky, bluish appearance of cartilage. Osteogenic sarcomata entirely consisting of myxomatous tissue are uncommon. More frequently myxomatous areas are found in tumors with an abundant admixture of cartilage. The presence of myxomatous tissue in the tumor is frequently accompanied with hæmorrhagic extravasation and this adds

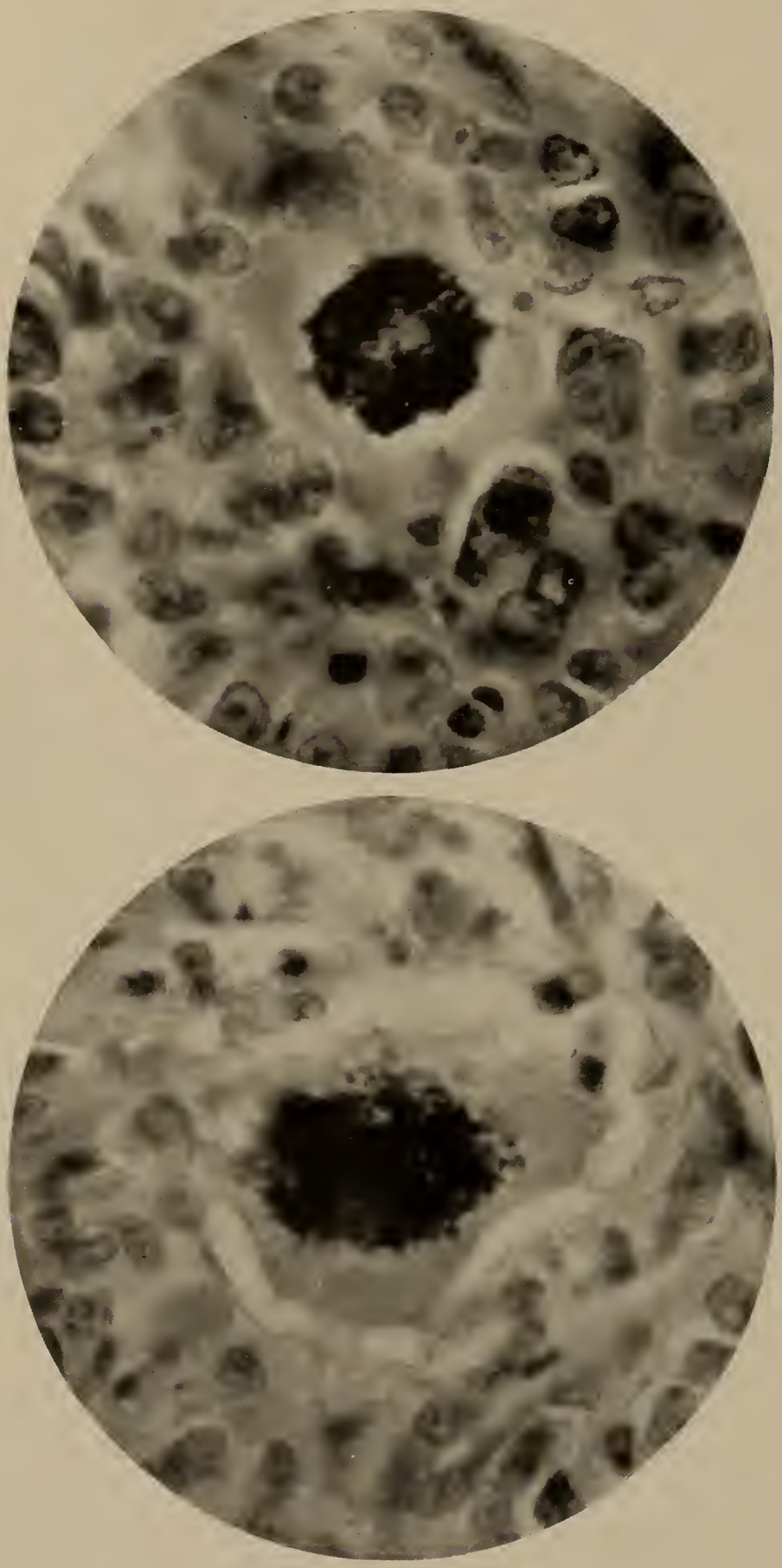


Plate 7. Case 49. Osteogenic sarcoma. Showing the huge amount of chromatin in the tumor cells passing through a mitotic stage.

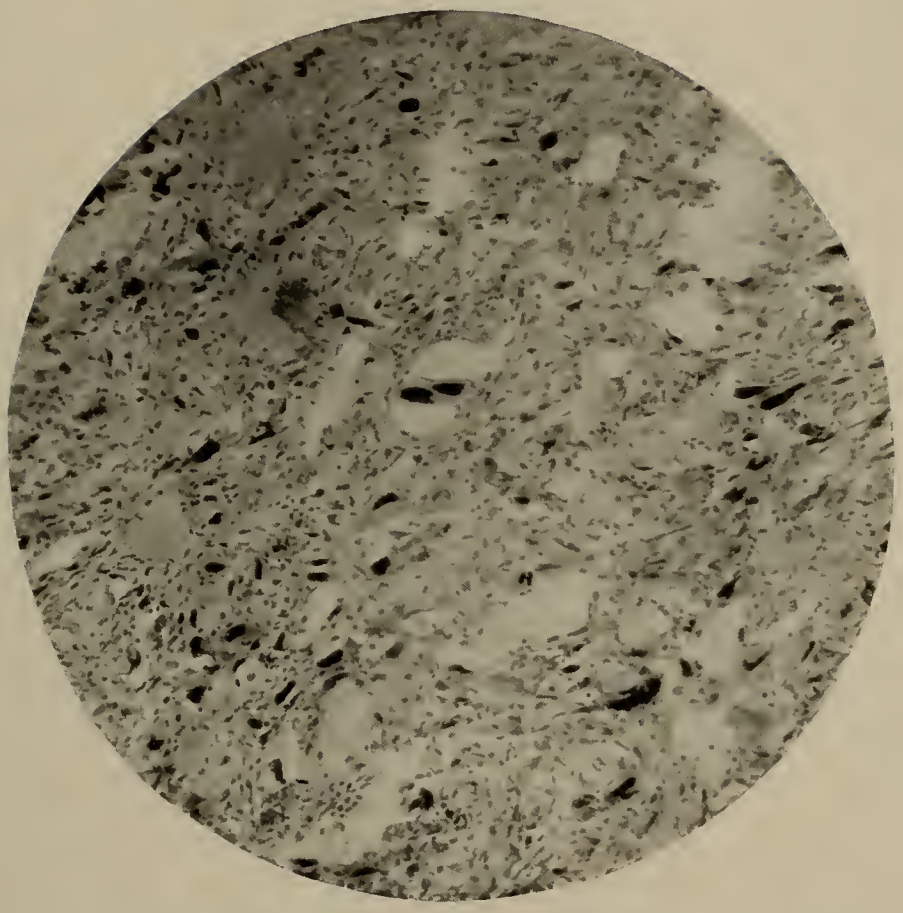


Fig. 14. Case 62. Osteogenic sarcoma. Showing mononuclear and polynuclear giant cells in a spindle cell stroma.

to the conspicuousness of the gross appearance of the tumor: blood clots, contrasted with soft, jelly-like, translucent, grayish-white tissue.

The fact that cellular areas can be found in definitely osteoblastic osteogenic sarcomata is of interest in relation to the idea, widely spread among bone pathologists, of a sclerosing type of osteogenic sarcoma. If true sclerosing osteogenic sarcomata do exist they are apparently a great rarity. In careful investigation of a tumor with the most pronounced dense shadow typical of sclerosing osteogenic sarcoma in the roentgenogram, cellular areas may be found with growth propensities typical of most malignant tumors. Cases have been observed in which along with a definite sclerosing character of the tumor in the roentgenogram cysts were present. It is best perhaps to draw an analogy between sclerosing osteogenic sarcoma and scirrhous carcinoma: the density of the stroma does not negate the presence of carcinomatous tissue.

The influence of the degree of vascularity of an osteogenic sarcoma on its consistency and gross anatomy is evident. In tumors with prevalence of cartilage and myxomatous tissue the blood supply is very moderate. In such cases the vessels usually run beneath the capsule of the tumor, the central portion of the tumor being poorly supplied. This is especially true of skeletal chondromata

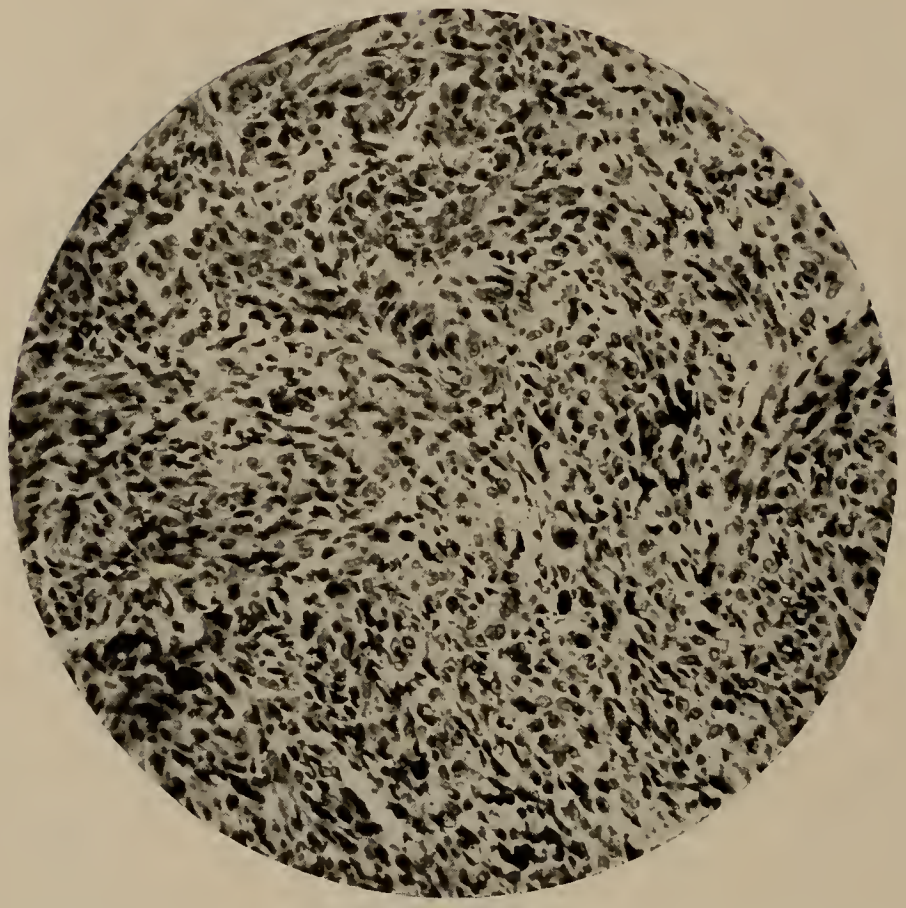


Fig. 15. Case 22. Photomicrograph of section taken from the same tumor as in Figure 16. Showing a lawless conglomeration of tumor cells; the intercellular substance is scant.

which have for many years remained benign and in which an incomplete surgical operation or trauma leads to an increase of the blood supply. Osteogenic sarcomata, which appear like such from the start, are usually very vascular; it is perhaps an analogy to the fracture-hyperæmia which is seen in young immature callus. With the further growth of the tumor the vascularity may change. It may decrease, especially in osteolytic tumors; or it may increase quantitatively and qualitatively—the number and size of the blood vessels may increase.

It has long been urged that cases with excessive vascularity be made a separate clinical and anatomical subdivision of osteogenic sarcoma. The main anatomical peculiarity of such a tumor is its rapid destruction of the involved bone. The destruction may extend along one of two ways: the shaft is simply absorbed and the whole tumor is enveloped in the periosteum with its thin bone capsule, or the shaft is rapidly perforated by the expanding tumor and is broken up in pieces. The remnants of the shaft may be found as sequestra surrounded by blood clots. The amount of tumor tissue present in such an osteogenic sarcoma varies greatly. Usually the cellular areas are quite extensive. In such cases there are no large blood spaces, but numerous small blood capillaries forming a

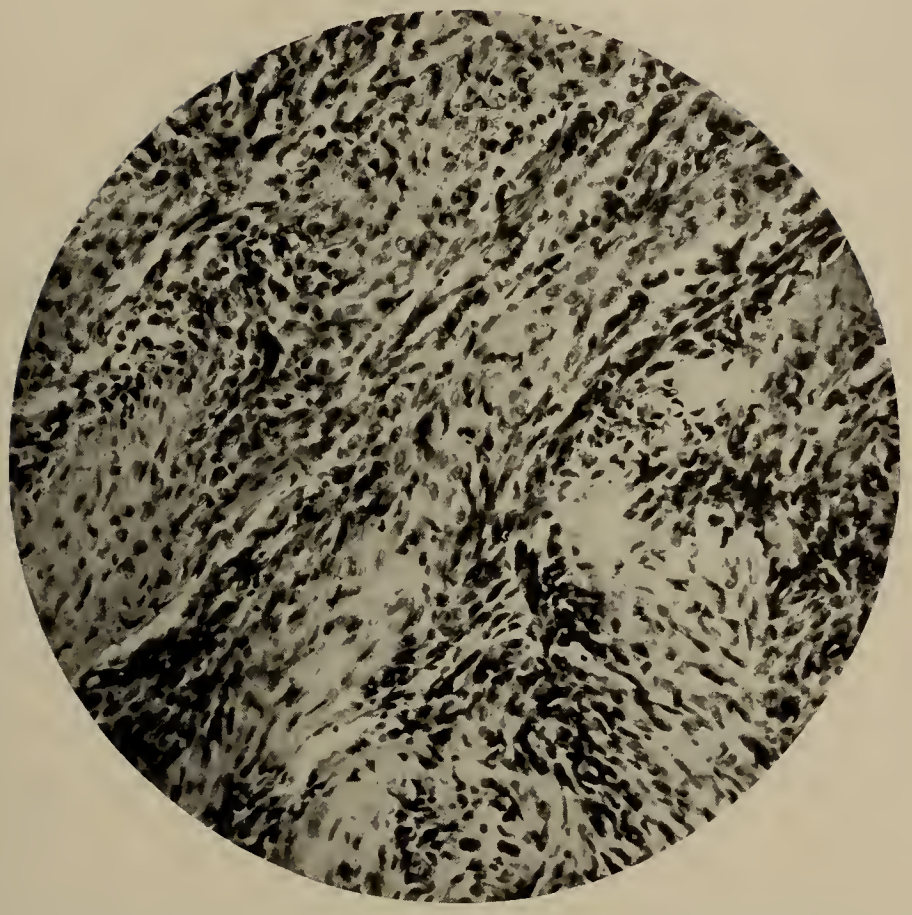


Fig. 16. Case 22. Compare with Figure 15. Osteogenic sarcoma. Showing an arrangement of the tumor cells in fasciculi; a visible amount of intercellular substance is present.

web-like net throughout the mass of tumor cells. Rarely in an osteogenic sarcoma the tumor tissue present is very limited and the entire tumor is constituted of thin walled alveoli surrounding wide blood spaces. Such tumors rapidly perforate the periosteal capsule, and then they may pulsate and even have a bruit (Plate 5). Despite the view commonly held that the telangiectatic osteogenic sarcomata give a poorer prognosis, there is no sufficient clinical evidence to bear it out. Neither clinically nor radiologically is it possible to make the diagnosis of telangiectatic osteogenic sarcoma. Only after the gross specimen is seen can such a distinction be made. The arguments for distinguishing telangiectatic osteogenic sarcomata as a separate entity are old. In 1879 Gross spoke of telangiectatic osteogenic sarcoma. His definition of this type of tumor was "sarcoma with excessive vascularity." The same definition though changed in words is still being given by all those who are urging the recognition of telangiectatic osteogenic sarcoma at this day. Vascularity alone is not sufficient to justify an exclusion of a tumor which is essentially a typical osteogenic sarcoma. It goes without saying that the definition "excessive" vascularity is very arbitrary and relative.

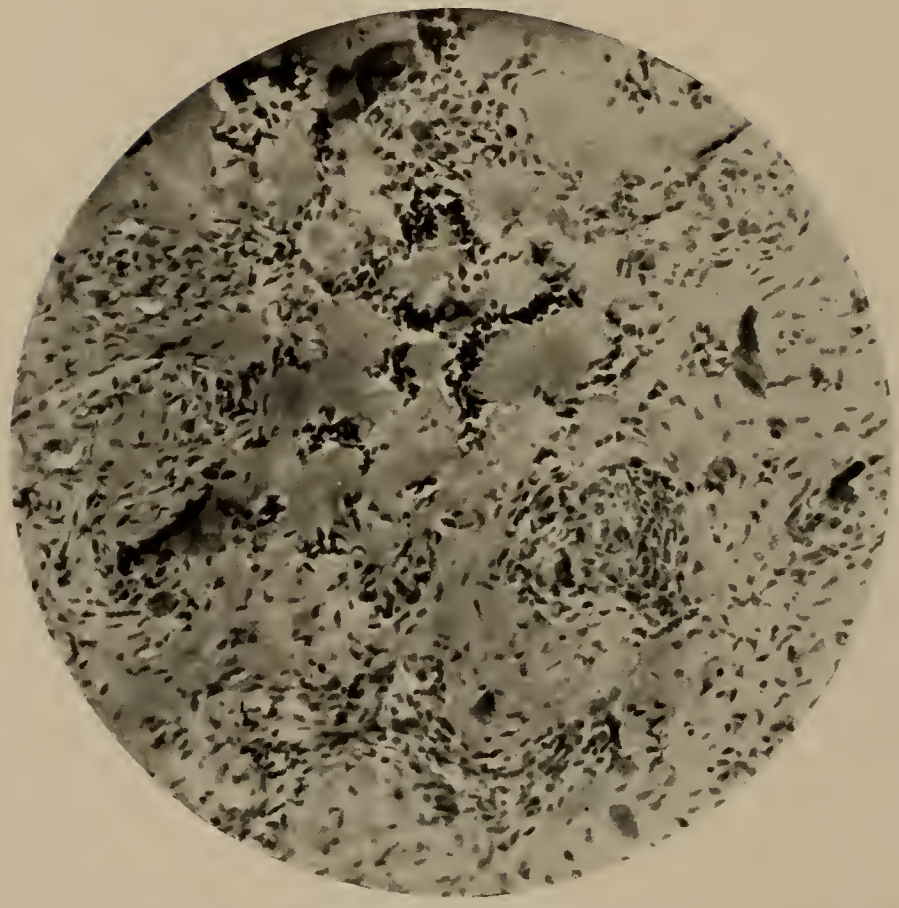


Fig. 17. Case 10. Osteogenic sarcoma. Showing a palisade-like arrangement of the tumor cells about hyaline masses.

The gross anatomical appearance of an osteogenic sarcoma may be greatly changed by regressive changes in the tumor. Because it is of importance to be able to diagnose an osteogenic sarcoma from the gross appearance, knowledge of the frequent degenerative changes occurring in these tumors is of interest. It should be kept in mind that these tumors are prone to degenerate with the result that the color may attain various shades from true fish-flesh to dark-bluish or reddish brown. The consistency may vary from that of the normally encountered resilient feel of liver to that of brain tissue, thin gelatinous substance, or even to fluid. Grossly necrotic tissue, mushy bone-marrow and even a pus-like mass mixed with bone sand are not uncommon findings. It is thought that the cause of degeneration is lack of living material in the rapidly growing tumor, but as a matter of fact degenerative changes frequently occur in very vascular tumors. Central medullary degeneration in osteogenic sarcoma may lead to cyst formation with subsequent perforation of the cortex and periosteal capsule and formation of an extensive extra-osteal tumor (Plate 6). Such tumors have been known for long as "malignant bone cysts," a loose term not in any way expressing the true nature of the tumor. It should be borne in mind by the pathologist and the clinician that radiation therapy also frequently leads to

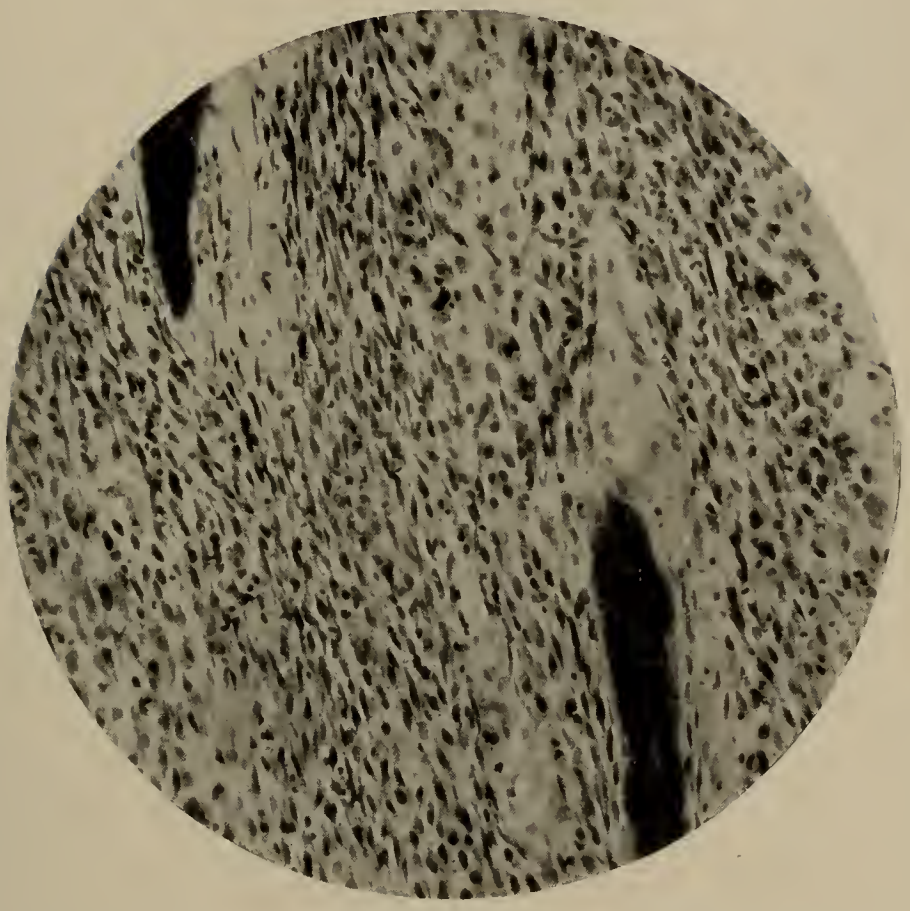


Fig. 18. Case 537. Osteogenic sarcoma. The tumor cells are surrounded by a hyaline intercellular substance ("near osteoid substance").

extensive degenerative changes and cyst formation (Fig. 10). The regressive changes following radiation of osteogenic sarcoma are so frequent and often so extensive that they deserve more attention from the pathologist and surgeon than is usually given.

Of interest are the gross anatomical features of the so-called recurring type of skeletal chondroma. The clinical features of this not infrequent tumor will be pointed out in detail in their respective places; suffice it to mention here that these tumors are characterized by their long duration before the onset of symptoms. An apparently benign tumor remains stationary for years until an incomplete surgical operation or some other kind of intervention (trauma) leading to an increase of vascularity of the tumor takes place, when the tumor rapidly acquires the characteristics of an osteogenic sarcoma. Grossly these tumors do not seem to involve the cortex at all. However, local recurrence and later metastases and death prove the malignant nature of the tumor. The tumor frequently reaches a very large size. The tumors have apparent capsules which are intimately attached to them. On the cut section, cartilage with calcified areas is seen; this explains the grating with which the knife cuts the tumor. Degenera-

Fig. 19. Case 216. Same tumor as in Plate 11. Osteogenic sarcoma. Showing the polymorphic variety of the cells in atypical "abortive" cartilage.

tive changes with cyst formation are frequent findings in these tumors (Fig. 11). That the pathologist and surgeon are not sufficiently informed about this type of tumor is judged from the instances of erroneous prognoses given.

Structure

The histological picture of the group of tumors designated as osteogenic sarcomata is most conspicuous and varied. It would be erroneous to attempt to give a typical picture of an osteogenic sarcoma. The large majority of osteogenic sarcomata are histologically atypical, or better still there is no one type of osteogenic sarcoma. Osteogenic sarcoma is a tumor derived from cells which are descendants of mesoblastic elements predestined embryologically to form bone, hence the cellular elements of osteogenic sarcoma have the potential ability to differentiate into osteoblasts. The ladder which leads the undifferentiated mesoblast up to the culminating point of differentiation—the osteoblast—has many rungs. The theoretical potential ability of the tumor cells to differentiate expresses itself in reality not in every individual tumor to the same degree. The apex of differentiation—the osteoblast—is the final goal which can be reached

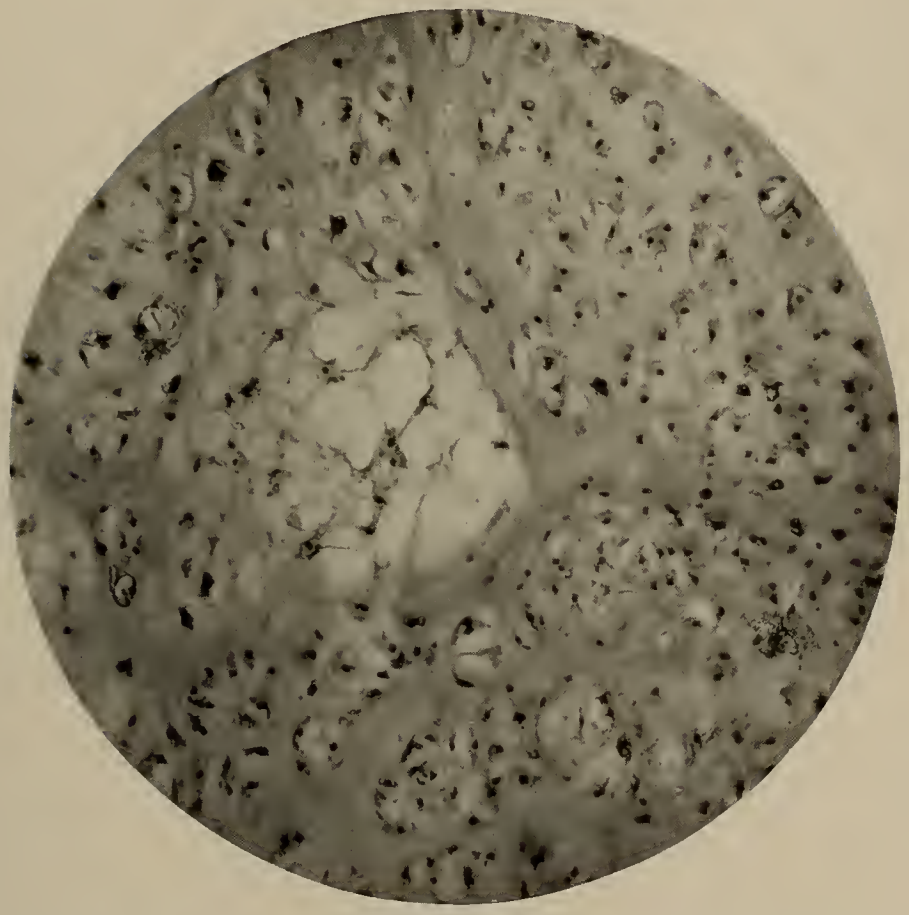


Fig. 20. Case 197. Section taken from the same tumor as in Figure 21. Osteogenic sarcoma. Showing atypical cartilaginous matrix with a beginning myxomatous degeneration.

by a tumor cell but which is not always reached. Something prevents the cell from further climbing up the ladder of differentiation and drives it to assume its lawless career. In almost every case of osteogenic sarcoma cells may be found which are arrested in their differentiation at various steps of the ladder.

It is easy to see how the numerous possible combinations of cells in various stages of differentiation lead to the many varieties of osteogenic sarcoma. The histological picture is still further complicated by the great variety of the intercellular substances. Here also several stages may be encountered in which the intercellular substances vary from simple fibrillation and hyalinization to true bone formation. The changes in the involved bone itself contribute greatly to the complexity of the histological structure of osteogenic sarcoma. The destructive and productive changes in the bone as a result of the aggression of the tumor are most complicated and interesting. Finally, the variety of the blood vessels and other peculiarities of osteogenic sarcomata emphasize the exceptional nature of their histology, as compared with other malignant tumors.

Through the collective studies of "bone sarcoma" by men associated with the Registry, it is possible today to state most definitely that two types of cells

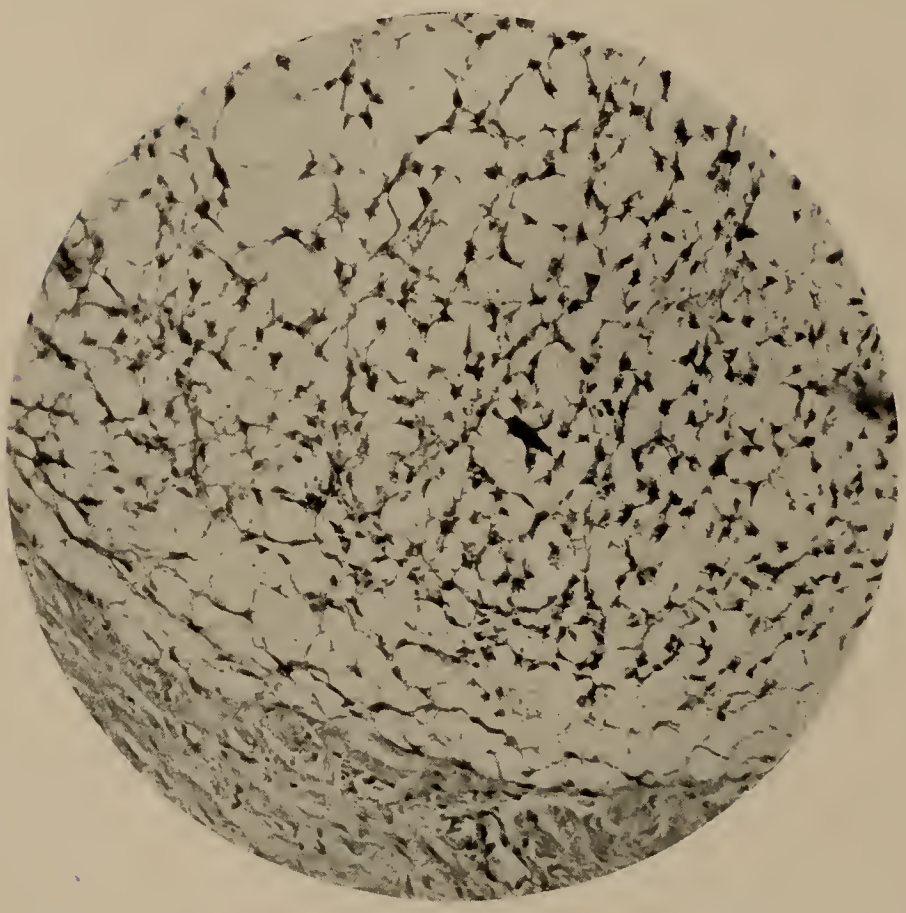


Fig. 21. Case 197. Compare with Figure 20. The myxomatous degeneration of the cartilage is completed.

which have enjoyed a most important place in the histology of osteogenic sarcoma according to former teachings do not really belong to the structure of osteogenic sarcoma. One of these is the giant cell of epulis type. Tumors consisting mainly of this type of cells are permanently excluded from the group of "bone sarcoma." The other type of cell is the round cell. It cannot be emphasized too strongly that osteogenic sarcomata are never of the round cell type. In other words, if the leading cell of the tumor is a round cell it is not an osteogenic sarcoma. Erroneous statements on the presence of round cells in osteogenic sarcoma are frequently due to the fact that the study given the tumor was not careful enough. This is especially true when the predominating cell type is the small spindle cell. In this the nucleus is small and hyperchromatic, and the cell borders are made out with difficulty, so that on cross sections such cells will easily simulate round cells.

The most frequent cell type in osteogenic sarcoma is the spindle cell. This is not surprising when one recalls that the spindle cell is the standard type of cell participating in normal bone repair processes. The most frequently encountered spindle cell is of the small variety with a small hyperchromatic nucleus with undistinguishable cell borders (Fig. 12). When the small spindle cells

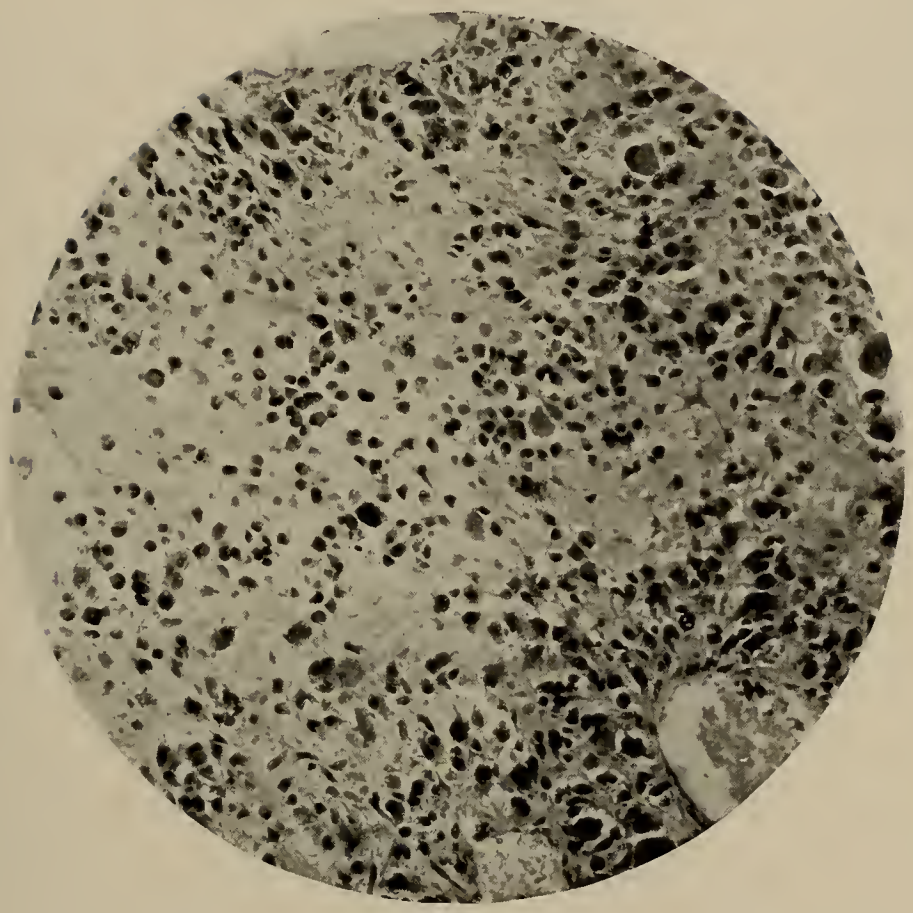


Fig. 22. Case 303. Osteogenic sarcoma. Showing cellular areas about the blood vessels and the relatively acellular cartilaginous matrix.

become larger, thicker, fuller, and plumper with bodies drawn out into filamentous processes we have the large spindle cells. With the further increase in size of the nucleus and the amount of the cytoplasm of these large spindle cells, when the filaments become detached from the cell, we have the polyhedral cells. There is very little morphological difference between such a polyhedral cell and a true bone cell. As in other rapidly growing malignant tumors one of the main characteristic features of the tumor cell is hyperchromatism. The chromatin in the nucleus—that morphological indicator of the growth propensity of the cell—is present here in large amount and causes a deep staining of the nucleus (Plate 7). It should be remembered, however, that hyperchromatism is of significance only when demonstrated in good technical hands; it is then a more important sign of malignancy than differentiation of the cells into fibers and bundles is a sign of benignity. Frequently the hyperchromatism observed is a result of old hæmatoxylin which requires a prolonged decolorization in acid alcohol. Variation in the size of the cells in the same tumor is very frequently encountered in osteogenic sarcoma. The chief feature of an osteogenic sarcoma arising in a persisting or recurring skeletal chondroma is the variation of the cartilage cells. The large polyhedral tumor cells frequent in tumors with a cartilaginous matrix

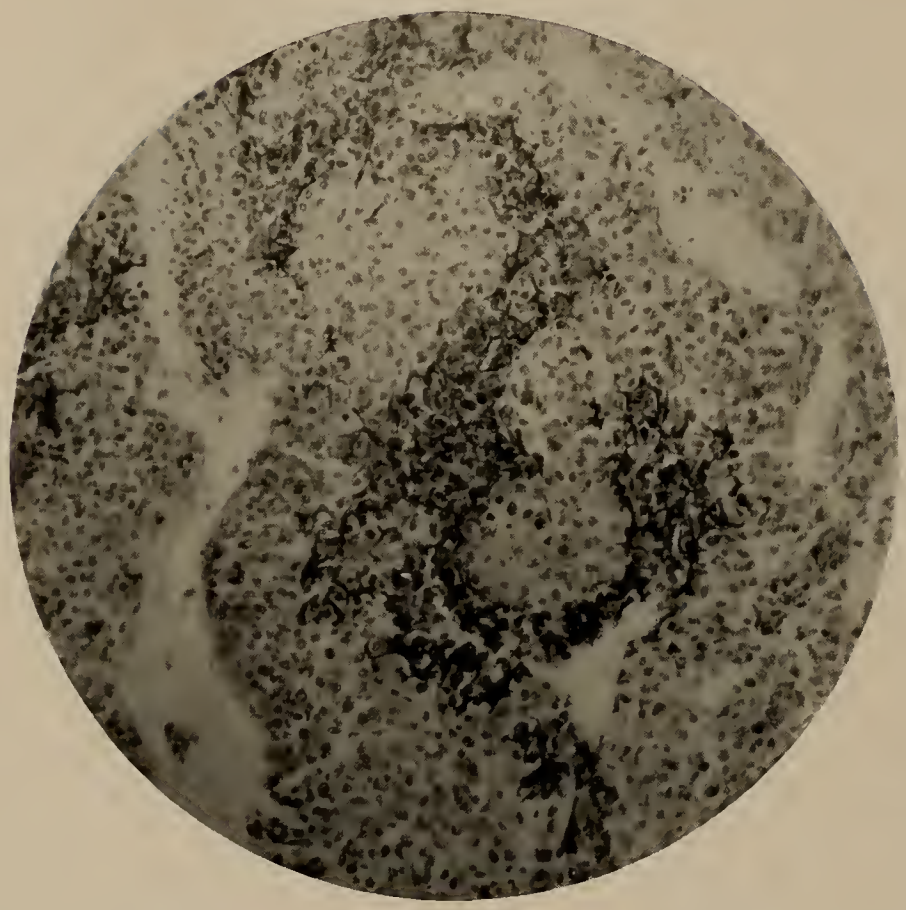


Fig. 23. Case 559. Osteogenic sarcoma. An early stage of ossification. The individual cells are surrounded by deeply staining granules marking the cell borders.

are said to originate from cartilage cells, or better, are undifferentiated cartilage cells (Fig. 13). Tumors of the great trochanter are noted for such cells.

Of much confusion has been the question of giant cells in bone tumors. Be it said at this time, and this applies to all types of bone tumors malignant and benign, that we have in the distinction between "tumor giant cells" and "giant cells of epulis type" a morphological feature of prime importance. It is not in the scope of this monograph to deal with fundamentals of general pathology with reference to histological distinction between these two kinds of giant cells. While giant cells of the epulis type may be met in most reparative processes of bone and in benign tumors and inflammatory processes, tumor giant cells are seen only in malignant tumors and especially in osteogenic sarcomata. The most frequent tumor giant cells are the so-called mononuclear giant cells, while polynuclear tumor giant cells are seen chiefly in very rapidly growing osteogenic sarcomata (Fig. 14). A warning should be inserted here as to the importance of finding of giant cells in tumors in which an exploratory operation was done previously; the benign granulation tissue in the infected operative wound in the explored tumor may easily show such findings. While not a con-

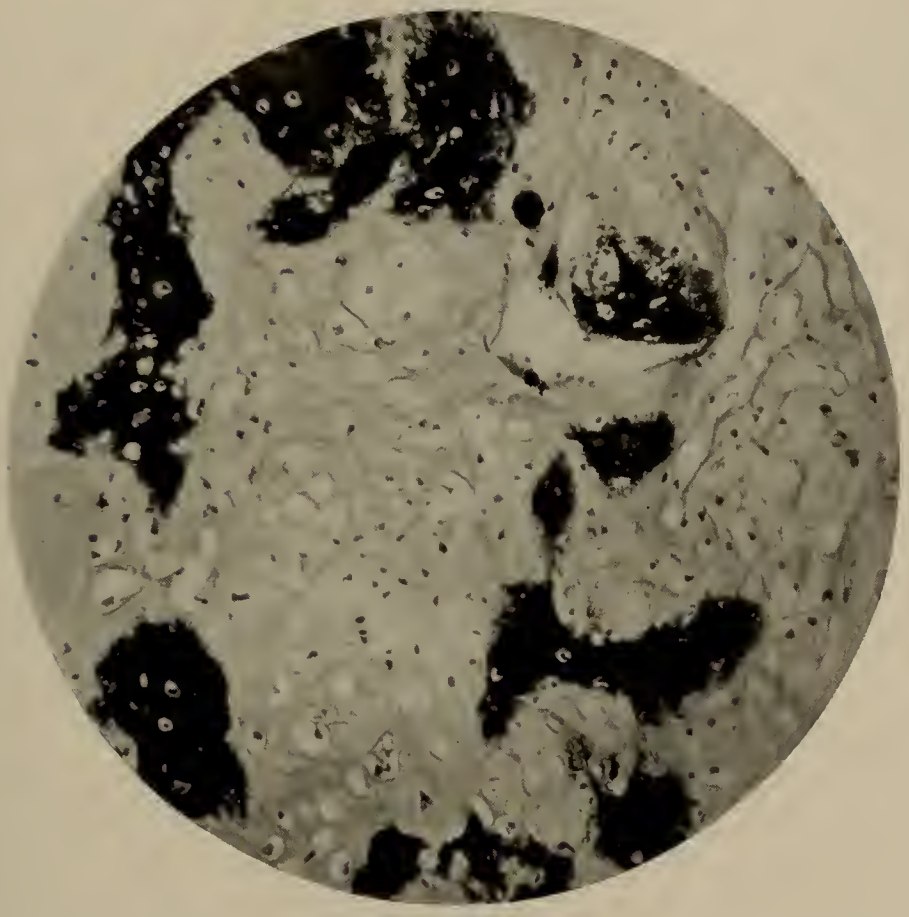


Fig. 24. Case 84. Osteogenic sarcoma. Further stage of ossification. The fusion of the granules leads to formation of bone trabeculæ.

stant finding, giant cells of epulis type are not infrequently seen in osteogenic sarcomata. Their numbers are sometimes so large as to awaken doubt in the inexperienced observer in the diagnosis of osteogenic sarcoma. In such cases a diagnosis of giant cell tumor is usually entertained. Another error is sometimes made when a tumor containing abundant giant cells and arising from tendon sheaths of fingers and toes is regarded as an osteogenic sarcoma of a phalanx. Giant cells of the epulis type are met frequently in far advanced cases of osteogenic sarcoma as a result of rapid and extensive bone absorption. These cells are not infrequent also in necrosing and suppurating areas of osteogenic sarcoma.

The chief morphological difference between osteogenic sarcoma and other malignant tumors is its intercellular substance. It is evident that with our methods of study of the intercellular substance being the same as those employed for study of the cellular elements we cannot expect to be greatly enlightened on this subject. If biochemistry is an integral part of biology, as indeed it is, it is here in the study of the intercellular substance that biochemical methods of investigation are urgently needed. Our knowledge of the intercellular substance, gained solely from morphological studies, is interesting in that it presents more clearly the whole process of development of osteogenic sarcoma.

Fig. 25. Case 273. Osteogenic sarcoma. Showing various stages of neoplastic ossification: fibrillation, hyalinization, and calcification.

All the varieties and shades of the intercellular substance encountered in osteogenic sarcoma may be grouped with one of the five types—hyaline, osteoid, cartilaginous, myxomatous, and osseous. To the hyaline type belongs not solely the hyaline homogeneous mass frequently seen in osteogenic sarcoma. The transparent sclerosed collagen fibers—the product of the filaments of the cell ends on one hand, and the homogeneous amorphous gelatinous mass on the other hand are best grouped with the pure hyaline intercellular substance. That the latter is a product of differentiation of cells normally striving toward bone production is evidenced by some interesting structural features of the tumors, especially well studied in the tumors of the spindle cell variety.

Sometimes in one and the same tumor, and always in a series of tumors, the leading tumor cell can be seen in one of four various arrangements. The first and most frequent finding is when the tumor cells form a lawless conglomeration without any visible order and without any seeming purpose of existence; the intercellular substance then is very scant and may be demonstrated only by special methods of study (Fig. 15). The next stage is when the cells evince some signs of beginning differentiation. The cells become arranged with their long axis in fasciculi, abundantly interwoven and interlaced among themselves

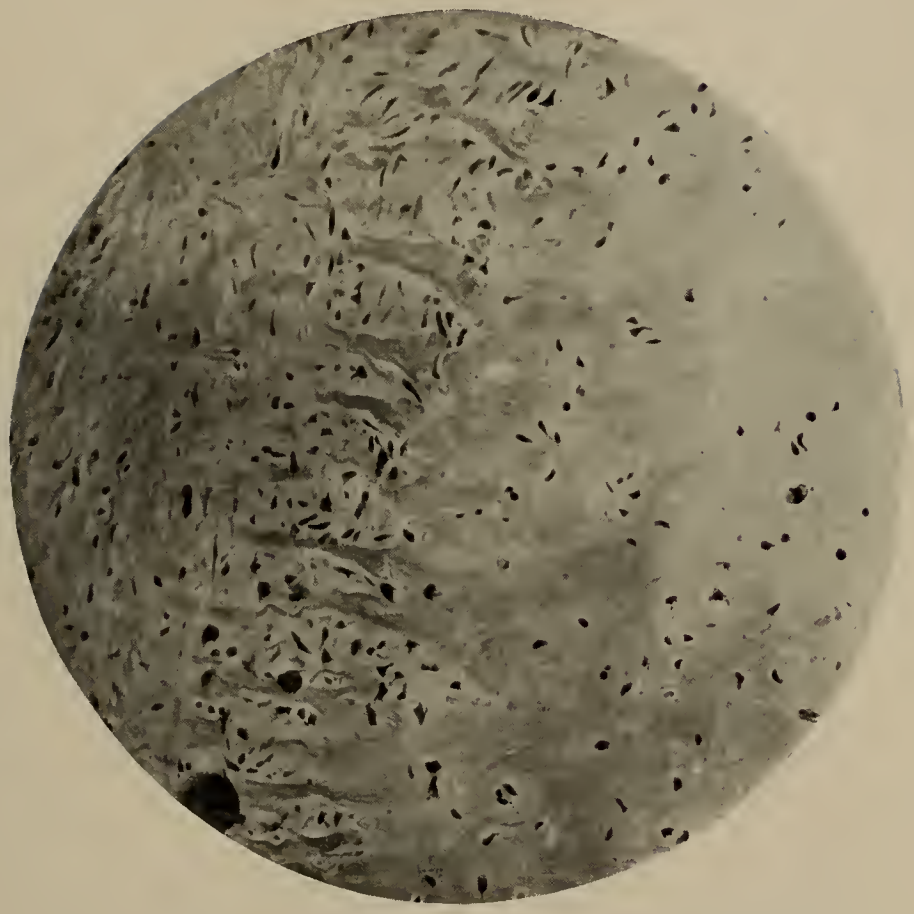


Fig. 26. Case 476. Osteogenic sarcoma. Showing intracartilaginous ossification in tumors with a cartilaginous matrix. Defibrillation of the matrix is followed by ossification.

(Fig. 16). They show a remarkable disposition to retain their arrangement, to which the easily demonstrable collagenous intercellular substance greatly contributes. These are the "bastard" osteoblasts. The third stage is a palisade-like arrangement of the tumor cells about hyaline masses. In cross section such groups of cells present easily distinguishable acini-like structures filled with hyaline substance readily stained with eosin light pink (Fig. 17). Further follow-up of these cells shows the last stage when the cells become surrounded by hyaline substance tending constantly to become more concentrated and by this time to show unmistakable signs of calcification (Fig. 18). The hyaline intercellular substance is a "near osteoid" substance from which the true osteoid matrix may form. In some cases of osteogenic sarcoma the less matured form of "near osteoid" substance prevails—a homogeneous amorphous gelatinous substance which is frequently erroneously interpreted as œdema of the tumor. "Near osteoid" substance is not an exclusive attribute of osteoblastic osteogenic sarcoma; it is not infrequently found in radiologically true osteolytic osteogenic sarcoma, an additional argument against attempts to make osteolytic tumors, mainly the medullary fibrosarcoma an entity distinct from osteogenic sarcoma.

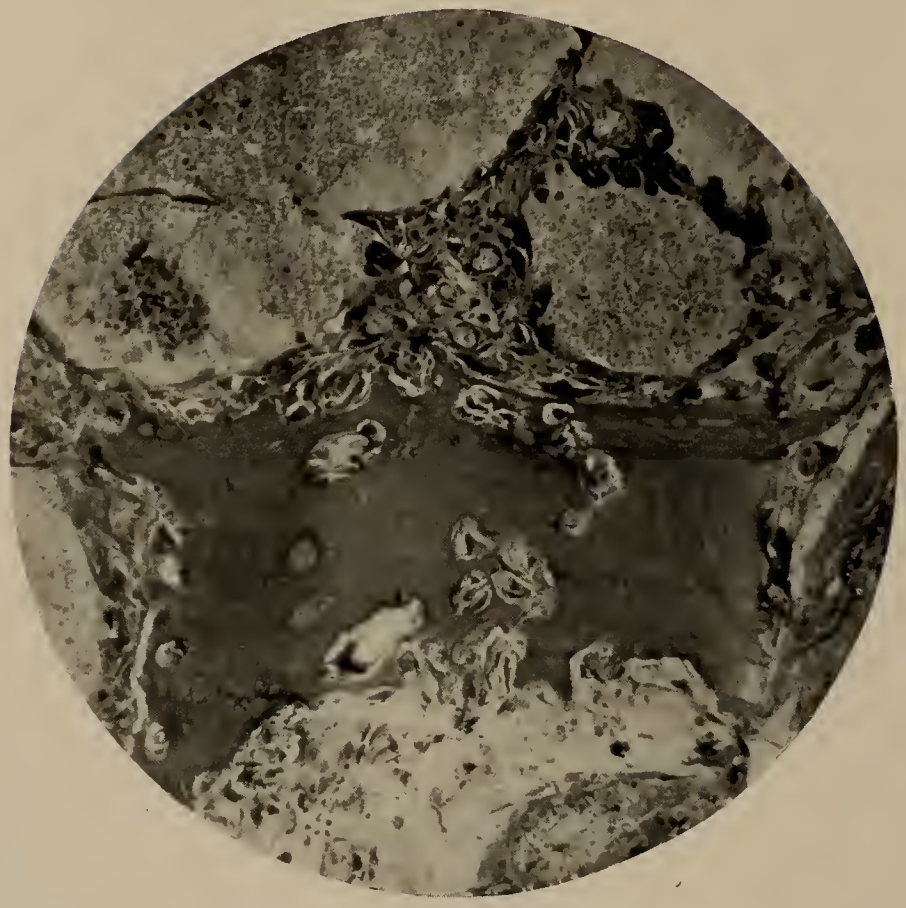


Fig. 27. Case 483. Illustrating the various modes of bone destruction in osteogenic sarcoma: bone destruction due to peripheral absorption, to vascular pressure, and to canalization by tumor cells.

When the hyaline matrix is abundant from the onset, it usually contains cartilage cells of varied size and shape; the ovoid and fusiform cartilage cell spaces contain one or more cartilage cells, mostly without capsule (Fig. 19). This is an abortive kind of cartilage when the pleomorphic character of the cells is the main sign of malignancy. Myxomatous tissue in osteogenic sarcoma is usually seen merely as a phase in tumors with an atypical cartilaginous matrix preponderating (Figs. 20 and 21). An intermingling of various types of intercellular substance in the same tumor is not uncommon in osteogenic sarcoma. The fact that all the tumor cells in the same tumor do not reach the same degree of differentiation at a given time easily explains why the same tumor produces condensation in the roentgenogram in one area and rarification of the shadow in another. The product of the cells of the same tumor may be osteoblastic, chondroblastic, and fibroblastic.

In osteogenic sarcoma with a preponderating relatively acellular cartilaginous matrix cellular areas may be seen closely surrounding vascular channels and spaces. These channels, usually blood capillaries, are in the center of the cellular areas while farther to the periphery avascular abortive cartilage is seen (Fig. 22).

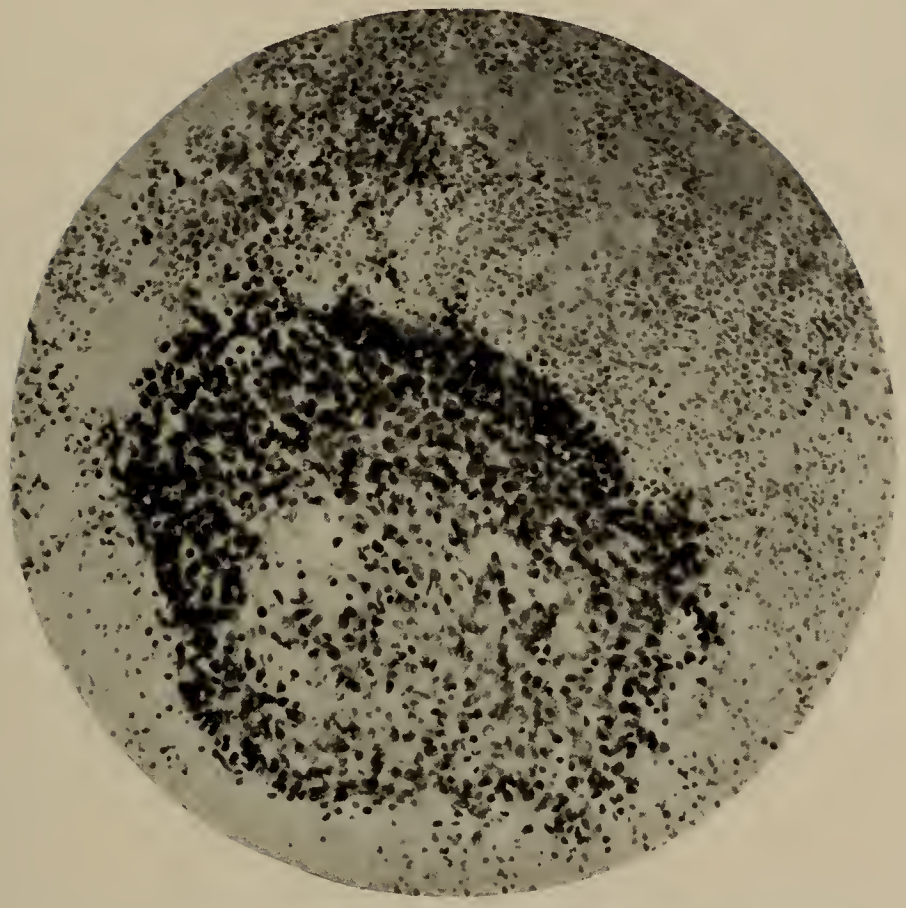


Fig. 28. Case 98. Same case as in Plate 5. "Telangiectatic" osteogenic sarcoma. Showing an island of tumor tissue loose in a blood space.

Whether these are conglomerations of tumor cells merely as a result of the proximity of a nourishment supply (vascular space), or whether the vessel is secondary to the accumulation of cells in one area, is a matter of speculation. In this connection it is interesting to note that the most frequent regressive changes in cartilage cells are the hydropic changes which are probably due to a discharge of water by the cell with precipitation following in it of water soluble constituents.

Some tumors which previously were believed to originate from periosteum, evince a remarkable disposition to ossification of their intercellular substance. They are sometimes known under the confusing name of osteoid sarcoma. These firm or soft medullary, brain-like, semifluid, or gelatinous tumors are traversed by numerous dense glistening striæ which are closely aggregated at their base on the bone surface. These spicules are mostly arranged perpendicularly to the surface of the involved bone; occasionally they pursue a course parallel to the periosteum raised from the bone by the expanding tumor. The fact that this parallel striation, although infrequent, does occur in osteogenic sarcoma, was entirely neglected by previous investigators.

The best explanation of the radiating striation in some osteogenic sarcomata is furnished by topographic-microscopical studies of such tumors. Microscopi-

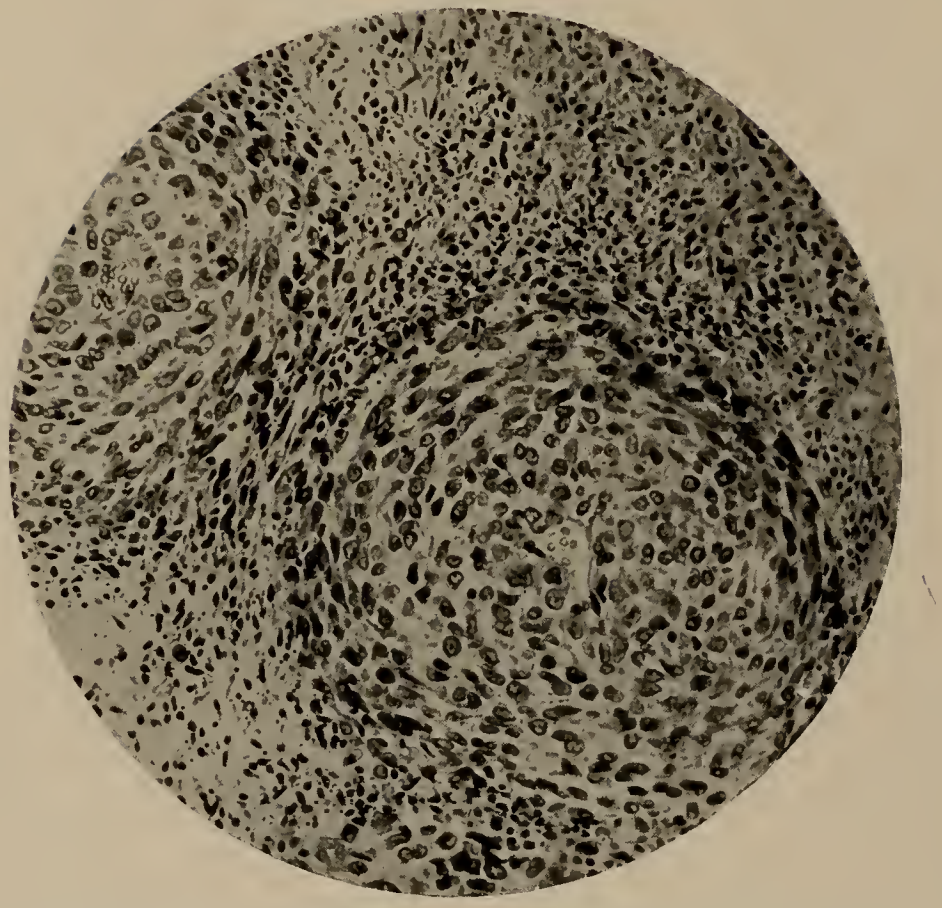


Fig. 29. Case 393. Osteogenic sarcoma. Showing the perithelial arrangement of tumor cells. The cells are in intimate proximity to the endothelium of the thin walled capillaries.

cally one sees dainty spicules attached by a relatively broad base to the cortex of the bone running perpendicularly to the elevated periosteum with its thin bone shell forming the investing capsule of the tumor. After approaching the periosteal bone shell, the spicule changes its course to one parallel with the periosteal bone trabeculæ, finally merging with the latter. The perpendicular striæ are connected among themselves by means of jagged, short, lateral ramifications. The striæ and their ramifications consist of osteoid or true osseous tissue. Tumor masses with thin walled blood vessels running parallel to the perpendicular striæ fill up the spaces between the spicules. From serial sections one gets the impression that the perpendicular blood capillaries emerge from the haversian system of the involved bone. When the periosteum is slowly being pushed away from the underlying bone by the expanding tumor the periosteal blood vessels entering into and arising from the haversian system are stretched in the direction perpendicular to the bone. Apparently the course of the blood capillaries defines the lines along which the osteoid tissue formation and ossification is to take place. That the blood vessels do play an important rôle in the arrangement of the striæ is suggested also by the fact that when the tumor perforates the investing perios-

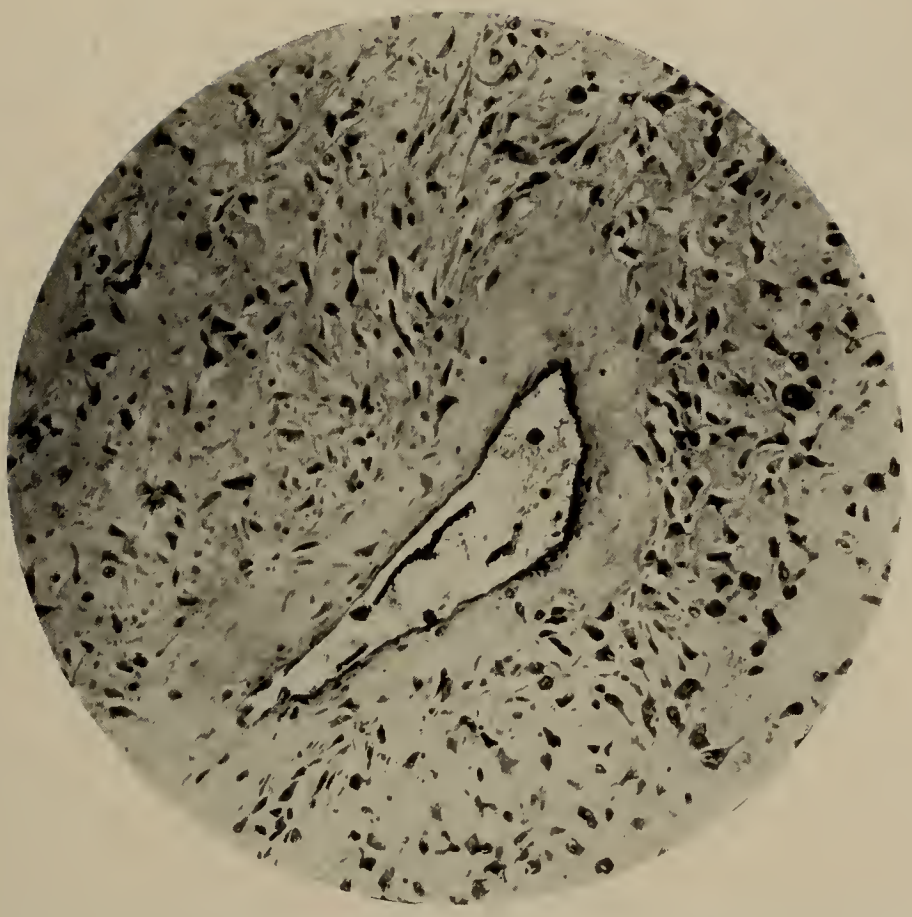


Fig. 30. Case 317. Osteogenic sarcoma. Showing a blood vessel lined by endothelium with a wall consisting of a homogeneous mass suggesting an osteoid or near osteoid substance.

teal capsule and becomes extra-osteal the radiating arrangement is mostly missing in the extra-osteal portion of the tumor with its disorderly arranged blood vessels.

Ossification of the intercellular substance in osteogenic sarcoma is the apex of differentiation which may be reached by the tumor cells and intercellular substance. The whole biological process of ossification is immensely complex and our knowledge of it at present is far from complete or satisfactory. Like normal ossification in the animal body, ossification in osteogenic sarcoma is known to us mainly in its morphological features which certainly are less important than the biological and microchemical features of this process. It is the degree of ossification in osteogenic sarcoma that draws the line between osteoblastic and osteolytic forms. After all, the whole difference is probably a chemical one; that it is not anatomical one sees from the rapid ossification which frequently sets in in an osteolytic osteogenic sarcoma after radiation.

According to morphological findings one meets in osteogenic sarcoma with two types of ossification—the metaplastic and neoplastic. When under certain favorable conditions, of the nature of which nothing is known today, an organic component added to the pre-existing fibrillar intercellular substance leads to

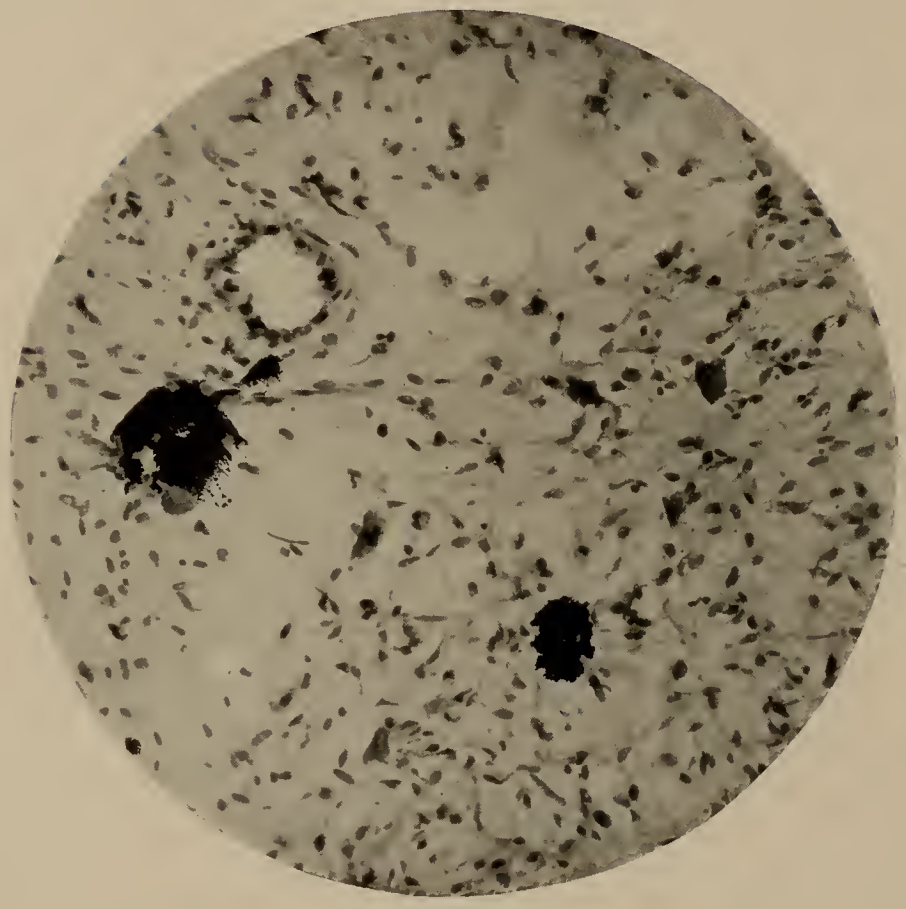


Fig. 31. Case 360. Osteogenic sarcoma. A blood vessel with a wall consisting of a myxomatous substance is seen.

homogenization and hyalinization of it with further calcification taking place, we have osseous tissue formed in the metaplastic way. The successive stages of the development of metaplastic osseous tissue is best studied on small islands of osseous tissue where the process of this form of ossification is in its very early stages. In sections through such areas in tissue undergoing metaplastic ossification one sees about the spindle cells embedded in a homogeneous intercellular substance numerous small cocci- and bacilli-like granules staining with hæmatoxylin deeply blue and with Van Gieson red. The granules are more numerous along the cell borders and decrease in numbers further to the periphery, disappearing entirely at some distance from the cell borders. One sees a picture resembling numerous small magnetic fields of influence with the cells in the centers (Fig. 23). At a later stage the granules continue to multiply and to join each other and soon the whole field is covered by a mass deeply blue in color with pale bone lacunæ occupied by the bone cells (Fig. 24). A certain constant relationship between this granulation and the blood capillaries can be made out. The blood vessels form the centers wherefrom the granules spread continuously. However, the immediate surroundings of the blood vessels are always free of granules even in the final stage of confluence of the granules and bone formation.

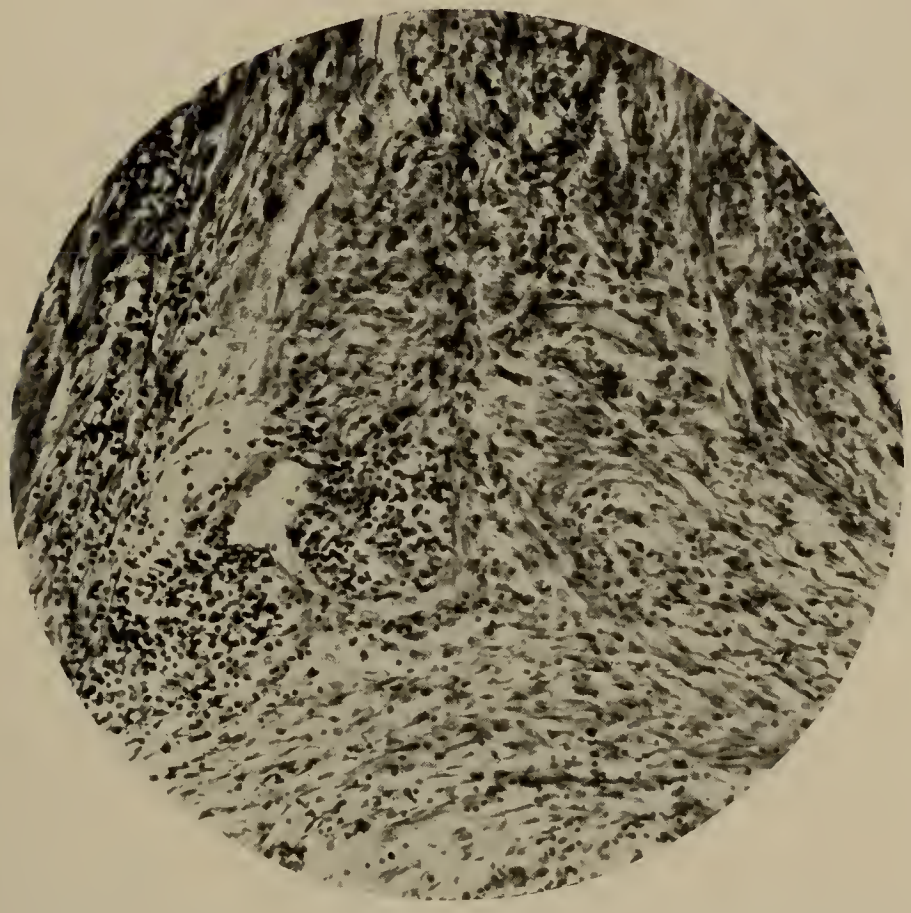


Fig. 32. Case 100. Showing a focal lymphocytic infiltration of an osteogenic sarcoma. (A 5 years' cure after amputation.)

That these granules are not precipitated calcium may be concluded from the fact that they are present in the sections after complete decalcification of the tissue. Seemingly the granules belong to the organic substances which are to be added to the pre-existing fibrillar intercellular substance for the process of metaplastic bone formation. The dependence of the granules upon the cells which they surround is seen from the fact that their number decreases with the increase of the distance from the cell. This would suggest that the granules are a product of a biological function of the cell; a function which appears in the cell as a result of some other biochemical process entirely unknown today.

The neoplastic ossification differs from the metaplastic chiefly in that in the former the fibrillar base for ossification is not pre-existing but is formed in the process of ossification by way of cell proliferation. Focal proliferation of spindle tumor cells, arrangement in rows with fibrillation and hyalinization and finally calcification are the main stages of neoplastic ossification in osteogenic sarcoma (Fig. 25). To the neoplastic ossification belongs also the not infrequent intracartilaginous ossification in osteogenic sarcoma with a rich cartilaginous matrix. The cartilage cells arrange themselves in columns separated by bundles of homogeneous fibrils invading the cartilage from the adjoining osteoid tissue

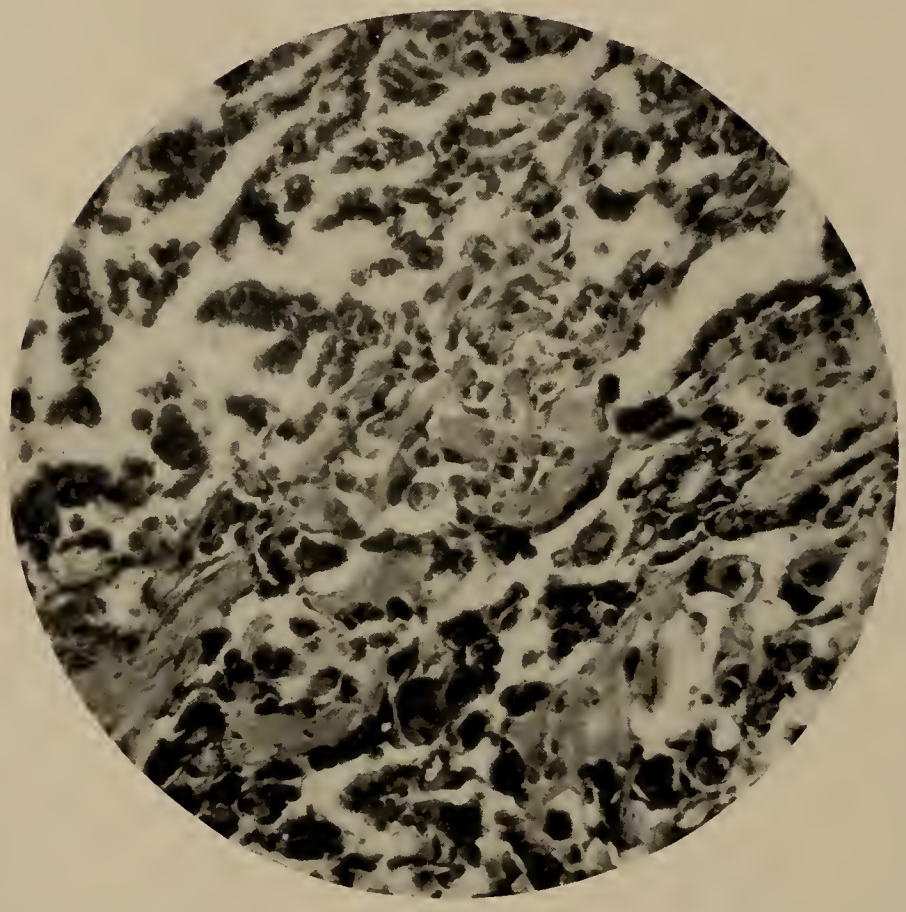


Fig. 33. Case 378. Showing hyalinization of the stroma of a lymph node metastatically involved in osteogenic sarcoma.

(Fig. 26). This defibrillation of the cartilaginous matrix precedes final ossification. In sections one frequently sees small cartilage islands surrounded by recently ossified tissue. In the course of time the remnants undergo the same fate while the older ossified portions slowly change their deeply blue color to a rose pink.

It would be erroneous to believe that it is always possible to draw a strict line between metaplastic and neoplastic ossification in general and especially in osteogenic sarcoma. It is not surprising to find in osteogenic sarcoma, that most perplexing malignant tumor of the human organism, not merely combinations between metaplastic and neoplastic ossification but also instances in which one can hardly decide where the neoplastic process stops and the metaplastic begins. After all, both these terms neoplastic and metaplastic are based merely upon morphological and not biochemical data.

Great importance has been ascribed to the discrimination in osteogenic sarcoma between bone formed by the tumor elements and that formed by the involved bone proper. In the literature and in the discussions on the Registry classification one finds the first referred to as tumor bone as contrasted with the latter as normal bone or reactive bone, i.e., bone formed as a result of a reactive

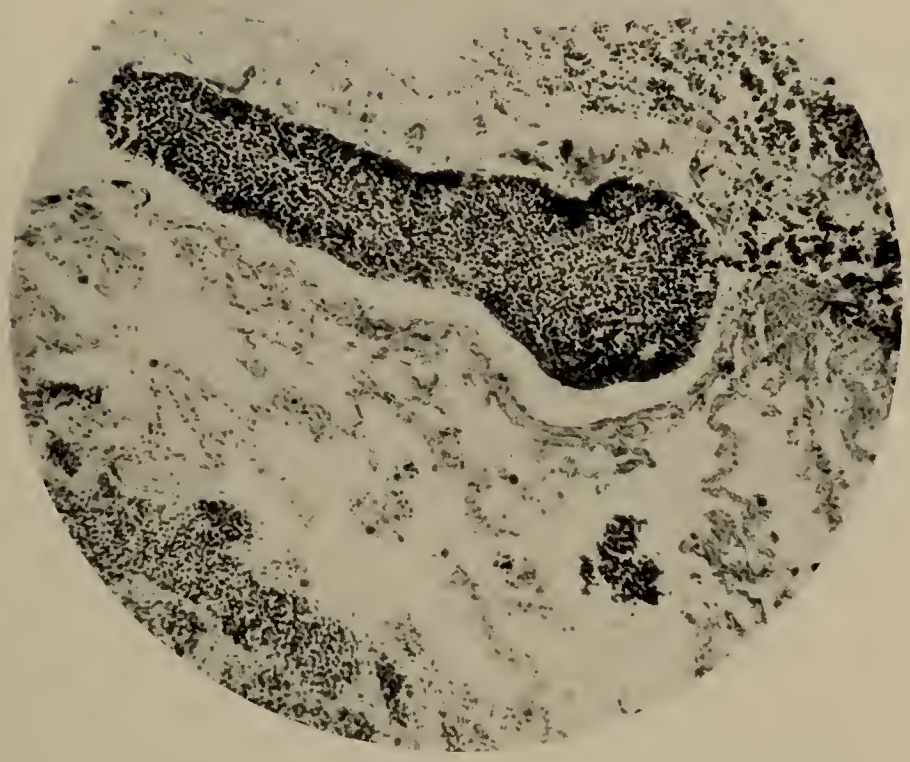


Fig. 34. Personal observation; case not registered. Pulmonary metastases in osteogenic sarcoma. Showing small nodules of tumor beneath the visceral pleura.

inflammatory process of the involved bone due to the presence of the tumor. There can be no two opinions about the fact that reactive bone as such does exist; it is a result of a proliferative reactive inflammatory process in the bone as a response to the involvement; on the other hand the whole discussion about tumor bone and reactive bone does not seem to be backed by morphological or biological evidence. The crux of the argument concerns the presence of two kinds of new formed bone in an osteogenic sarcoma—lamellary bone and trabeculated. Under lamellary bone one understands bone composed of parallel lamellæ supplied with typical bone cells inclosed in bone lacunæ. This is the characteristic structure of the physiologically normal bone. The trabeculated type of new formed bone shows irregular, mostly homogeneous or fibrillar osseous trabeculæ, staining deeply blue with hæmatoxylin, usually lacking the lamellary structure. For long the general belief was that tumor bone is always trabeculated as contrasted with reactive bone which is always lamellary. This discrimination against trabeculated bone apparently is founded on the erroneous statement of Kaufmann many years ago, which identified lamellary bone with bone produced by osteoblasts (*osteoblasten Knochen*). That reactive new bone may be

Fig. 35. Case 457. Osteogenic sarcoma. Advanced pulmonary metastases.

trabeculated we see in new bone formation in metastatic carcinoma, all the new formed bone being reactive bone and not tumor bone. Trabeculated bone is frequently seen also at some stage or other of callus formation in the process of normal fracture healing. On the other hand I have seen cases of osteogenic sarcoma in which areas of bone formation in the pulmonary metastases could well serve as illustration of normal lamellary structure of bone. Apparently the age of bone has much to do with the lamellation; in the slowly developing bone in pulmonary metastases there is ample time for the lamellary structure to take place, while in the very active process of callus formation much bone remains for a time trabeculated. It is not to be understood that in my opinion tumor

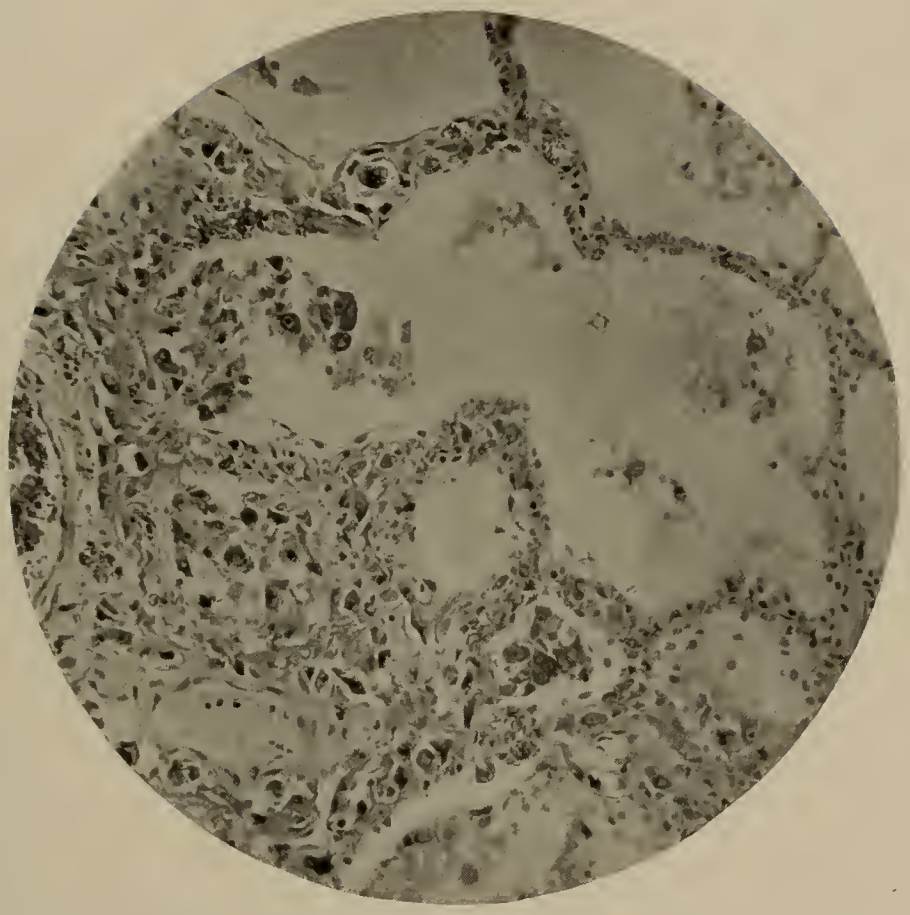


Fig. 36. Case 610. Same case as in Figures 37 and 38. Osteogenic sarcoma. Showing pulmonary interalveolar capillaries stuffed with tumor cells.

bone and reactive bone are entirely identical in every way; it is my belief that with the present day meager knowledge of the ossification process and the inadequacy of purely morphological studies of ready formed bone there is no dependable way to distinguish between tumor bone and reactive bone.

In general there is no essential demonstrable difference in the morphology between the normal physiological apposition of bone and the reactive or defensive production of bone. It was thought erroneously that the new bone is formed from the old. This conclusion is based upon the fact that wherever formation of new bone is following closely absorption of trabeculæ of the old bone, the new bone is seen closely attached to the old surrounding it. A distinction between the old and new formed bone is best reached after staining with hæmatoxylin—the old is red and the new is blue. In cases with very active new bone formation one can frequently find large groups of numerous osteoblasts—"osteoblast reserves" still unarranged but ready to defend the bone against the tumor. These polyhedral cells with relatively large nuclei appear suspicious to the inexperienced, and diagnoses of malignancy in giant cell tumors after radiation have been based upon the presence of such groups of cells along the regenerating bony capsule.

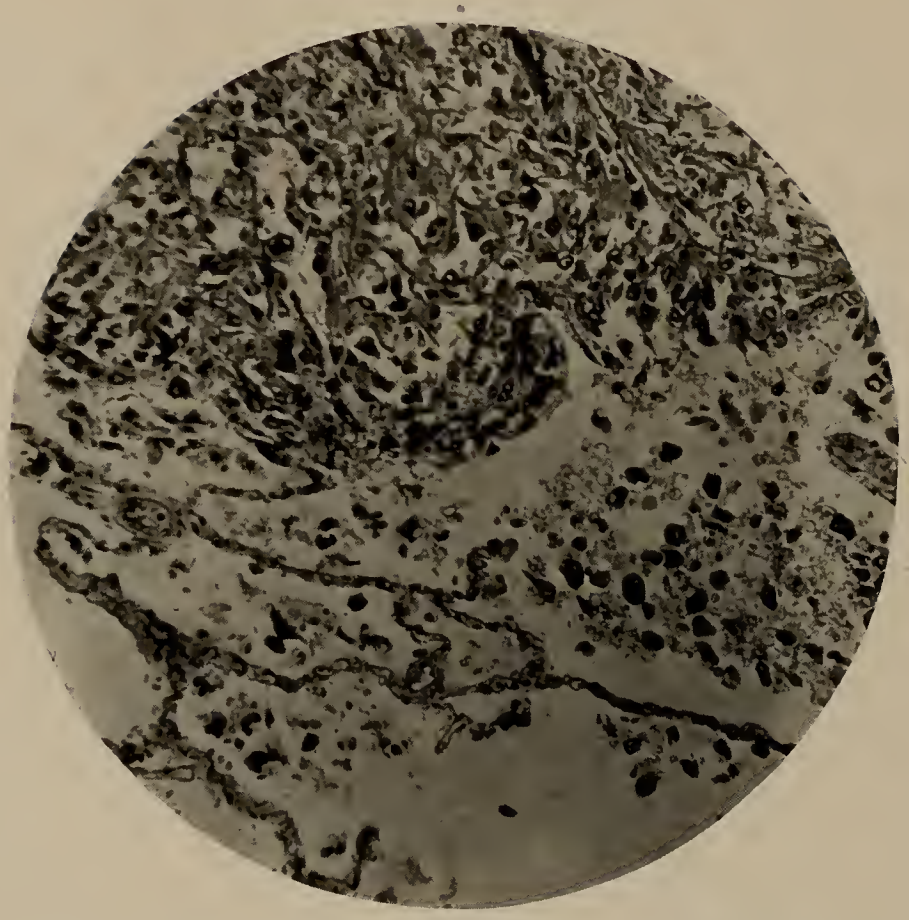


Fig. 37. Case 610. Compare with Figures 36 and 38. Pulmonary metastases with alveoli filled with tumor cells; the alveolar texture of the lung is obscured.

The inelasticity of the normal bone would prevent the growth and expansion of an osteogenic sarcoma if it were not for the destructive process exerted by the tumor upon the involved bone. The absorption of bone under the aggression of an osteogenic sarcoma is accomplished in several ways. One way is the lacunary absorption of the bone; this is the way occurring in the normal process of bone resorption. In osteogenic sarcoma, however, the lacunæ are more flat and small than in normal absorption. This difference is due to the fact that instead of large osteoclasts the tumor cells are found in the lacunæ. That the tumor cells are capable of absorption of normal bone is not at all peculiar to sarcomatous cells; in certain inflammatory conditions one frequently encounters absorption of bone without the typical osteoclasts. Typical polynuclear osteoclasts are usually seen when the destruction of bone proceeds slowly. Absorption may proceed simultaneously from the periphery and from the center of bone trabeculæ. The osteoclasts in the central area are tumor cells which have reached their place by way of newly formed canals as pointed out later. Another means of bone destruction in osteogenic sarcoma is canalization of the bone by advancing blood vessels. These are the Volkmann's canals existing in normal bone but

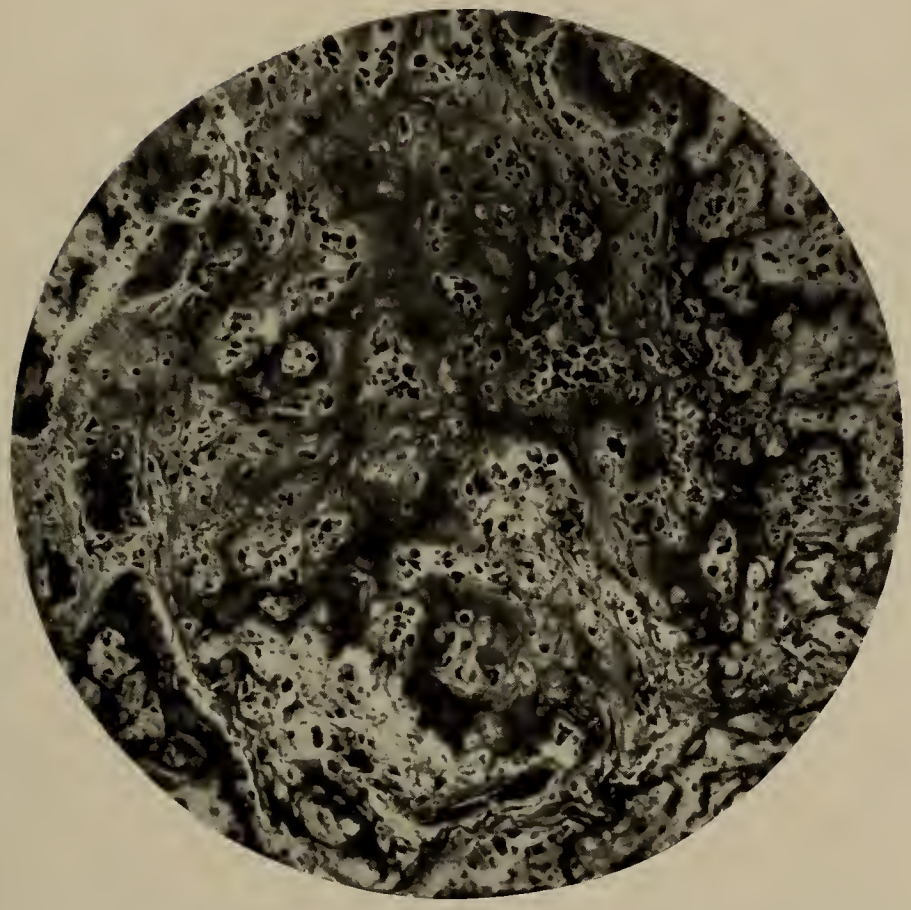


Fig. 38. Case 610. Compare with Figures 36 and 37. Pulmonary metastases with bone formation.

more numerous in a bone involved by an osteogenic sarcoma. Destruction of bone is also a result of an extreme vascularization of the tumor mass. Direct pressure of the numerous pulsating blood channels on their bony capsule leads to a rapid destruction of the bone. This explains the rapid destruction and not infrequent sequestration of large portions of the involved shaft in very vascular, so-called telangiectatic osteogenic sarcoma. Similar to bone destruction by canalization with blood vessels is that by canalization with columns of tumor cells. Through such new formed canals as well as through numerous new and old blood vessels and through the normal haversian system tumor cells cause minute communications between the medullary cavity and the subperiosteal space, leaving an apparently grossly intact shaft. By all these means the tumor gains ground and space in the involved bone (Fig. 27). The bone cells, released from their seclusion in the bone lacunæ after absorption of the bone do not seem to play any active rôle in the pathological process.

The peculiarities of the vascular system constitute one of the characteristic features of osteogenic sarcoma. In the first place the richness in vessels of an osteogenic sarcoma is interesting. These neoplasms are far better supplied with blood channels than normal bone. The only exception is found in osteogenic

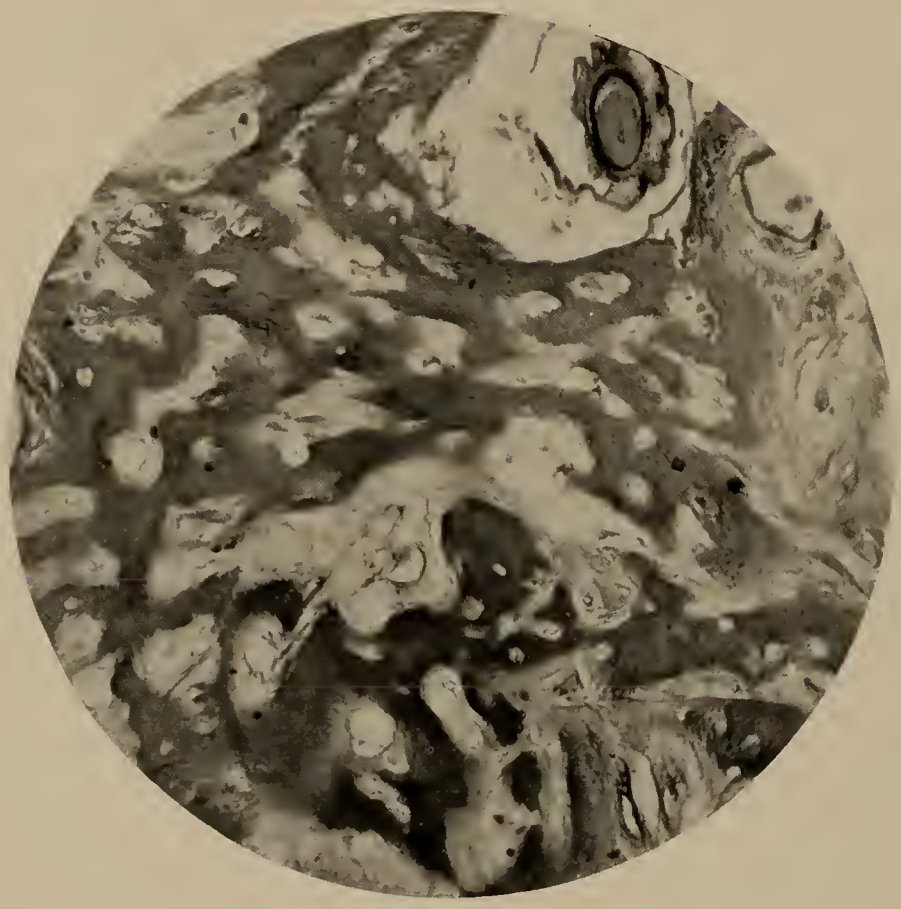


Fig. 39. Case 335. Showing metastases of osteogenic sarcoma to the skin; ossification about a hair follicle is seen.

sarcoma with a pure cartilaginous matrix as a base. The excess of vascularity may be seen also in the structures close to the tumor capsule where numerous, large blood vessels are seen. There was occasion to mention above the probable increase in malignancy of an extremely vascular osteogenic sarcoma. A telangiectatic osteogenic sarcoma is not more malignant because this is an essentially different disease but merely because abundant vascularity is a sign of lack of differentiation of the tumor growth, and as such it is a direct sign of greater malignancy. This suggestion is also supported by the fact that the blood vessels are the centers of very loose cellular areas (Fig. 28). The stage of differentiation is the higher the further the given area is from a blood vessel. This is also true of certain other skeletal dystrophies: sclerosis and ossification are usually at some distance from blood vessels. Calcification is apparently slowed down by the presence of blood vessels.

The blood vessels in osteogenic sarcoma are conspicuous in their anatomical structure and in their relationship to the tumor tissue. In the average pleomorphocellular osteogenic sarcoma numerous blood capillaries may be seen coursing along clefts between tumor cells. The tumor cells seem to carry the function of the endothelial lining of these blood channels. The same relation to the tumor

may be frequently noticed in blood vessels of larger caliber. Areas can be seen where cells of exactly the same morphological structure and appearance are lining blood vessels in one field and are indulging in bone formation in another. In still other places the endothelial lining of blood vessels seems normal but the wall consists of a homogeneous mass exactly like osteoid or near osteoid tissue (Figs. 29, 30). It is also not uncommon to find a cartilaginous matrix in place of the homogeneous mass forming the wall of the blood channel (Fig. 31). The lining of a capillary with tumor cells raises the question of the origin of such a capillary. If the capillaries here are formed according to general histological rules then they are formed by sprouting of a column of tumor cells, in other words there must be a most intimate relationship between normal endothelial cells and the tumor cells. These peculiarities of the blood vessels encountered in osteogenic sarcoma have been especially emphasized by Codman, who suggests for these the term "tumor blood vessels." Codman sees in these peculiarities a proof to his statement that the malignancy of bone sarcoma lies not in a certain kind of tumor cells but in the intimacy of the cells to the blood vessels. He suggests the idea that all osteogenic sarcomata are endotheliomata because, he thinks, the tumor cells spring from blood vessels as leaves from a tree. Whatever one's opinion may be, about Codman's broad statement, there is probably more truth than error in a belief that the malignant impulse imparted to the cells of a sarcoma lies much further back than in the origin of a "malignant set of cells." It may reside in a disorder of the laws of growth.

A peculiarity in the histology of osteogenic sarcoma which deserves special emphasis is a spontaneous lymphocytic infiltration (Fig. 32). A lymphocytic infiltration is not uncommon in tumors after radiation therapy. It is also frequent in osteogenic sarcoma in which an exploratory incision was made previously; it then being a simple inflammatory reaction to the infection brought in during the operation. A spontaneous lymphocytic infiltration however is not frequent; it is met with in about 5 per cent of all cases. That the lymphocytes are not an integral part of the tumor one can conclude from the fact that they are usually found on the periphery of the tumor. In the 17 cases with a five years' cure of primary malignant bone tumors registered, the majority of osteogenic sarcomata showed a marked lymphocytic infiltration, although several of these have had previous operations. This fact raises the question whether the lymphocytic infiltration is not an equivalent of the feature encountered in early carcinoma as pointed out by Paltauf. The latter called attention to the fact that in early carcinoma there may be found a lymphocytic infiltration of the surrounding connective tissue, which according to him is a result of the reaction of the organism to the carcinomatous involvement. The same feature may be evinced by early metastatic carcinomatous involvement of regional lymph nodes while in similar involvement of an advanced carcinoma this reactive process is

absent. "Unwillingly one gains an impression that the organism has lost its resistance and the carcinomatous cells gained the upper hand." Ewing suggested the advisability of a separation of all cases of osteogenic sarcoma with a lymphocytic infiltration from the general group. However, not all cases with a lymphocytic infiltration in the Registry gave a five years' cure.

The remarkably high malignancy of osteogenic sarcoma is due to a generalization of the tumor by way of metastatic deposits in other organs. No rules can be made as to the localization of the secondary tumor growths. They are known to occur in organs of the abdominal cavity, in the brain, in other bones and even in the skin; but the most frequent, the classical seat of a metastatic osteogenic sarcoma is the lungs. Death from the development of pulmonary metastases is the outcome in a very large majority of cases of osteogenic sarcoma. A metastatic involvement of the regional lymph nodes is rare. Frequently it is difficult to decide from the section alone whether the lymph node does show a metastatic involvement; occasionally an extensive hyalinization of the stroma of the enlarged lymph node is the only sign of a metastatic involvement (Fig. 33). The metastatic growth usually shows a tendency to turn to a less differentiated and more cellular structure than in the primary tumor. On the other hand in anaplastic metastases most complex pleomorphic tumors may become simple. Usually the cells of the secondary growth may reach all the various stages of differentiation as seen in the primary tumor and it is not unusual to find a metastatic growth with all the varieties of structure of an osteogenic sarcoma.

Pulmonary metastases have a tendency to grow slowly. Cases are known in which the haversian canals of the bone found in pulmonary metastases contained a structure strongly suggesting bone-marrow. A study of a lung involved metastatically in osteogenic sarcoma may show all the successive stages of the development of the metastatic growths. The first localization of the metastases is in the subpleural portion of the lung (Fig. 34). Here, right beneath the pleura, can be seen later the typical grayish-white rounded nodules of various size and of a consistency ranging from that of brain tissue to a solid, hard, ivory-like mass (Fig. 35). The tumor cells brought in the blood stream are retained in the interalveolar capillaries of the lungs (Fig. 36). In section one sees capillaries completely stuffed with tumor cells. Soon the tumor cells break through the wall of the capillary and begin to infiltrate the alveoli. The alveoli are seen packed with tumor cells (Fig. 37). Then the interalveolar capillaries become obliterated, and it is with difficulty that one makes out the alveolar texture. The whole area is converted into a tumor mass, with very faint traces of former alveolar structure of the lung. At a later stage bone may form throughout the mass (Fig. 38). A compensatory emphysematous dilatation of the adjoining alveoli completes the picture. Although uncommon, metastases to the skin with bone formation are known to occur (Fig. 39).

Clinical Course

A study of the clinical course of the primary malignant bone tumors has always attracted much less attention than the morbid pathology of these tumors. The explanation of this probably rests with the fact that the clinician was and still is helpless when confronted with primary malignant bone tumors. Even today the average clinician will gladly shift the task of diagnosis in such a condition to the roentgenologist and pathologist. A great deal of confusion in our knowledge of the clinical course was brought in by those who in their earnest attempts to give a description of the clinical course of these conditions have dealt with the primary malignant bone tumors as a whole, that is, as with a single clinical entity. Not less harm has been added by individual reports of single cases which erroneously were considered as "bone sarcoma." Clinical histories are not always properly taken in these conditions and the clinician does not pay sufficient attention to the history in the diagnosis. A complete, well taken clinical history very frequently can decide the question of the diagnosis in cases histologically obscure. Often from a good clinical history and roentgenograms one can be as sure of a diagnosis as from seeing the patient, the lesion, the gross specimen and numerous sections.

The incidence of primary malignant bone tumors is best seen from the fact that about one case out of three of sarcoma of the human body is a "bone sarcoma," the next in frequency being lymphosarcoma. From a careful survey in the State of Massachusetts, which, due to the influence of Dr. Codman, is the best educated in registering its cases of "bone sarcoma," it is estimated that the clinical incidence of "bone sarcoma" is about one to 100,000 of population at any one moment. According to recent estimates of English observers, there is in England about one case of bone sarcoma to 75,000 of population. Judging from the data of the Registry there occur about twice as many primary malignant bone tumors as benign giant cell tumors. According to these calculations there are about 1,100 to 1,450 patients with "bone sarcoma" alive at any one time in the United States. Allowing about one-third of this number fo the benign giant cell tumor and considering the average life of a patient with a true malignant bone tumor to be 5 years, we have about thirty thousand deaths from sarcoma in a generation (60 years), deaths in individuals mostly in the prime of life.

Social conditions have no influence as an etiological factor and cases of this disease are found in all walks of life. Of no great influence also seems to be sex, although the male sex is predominating in osteogenic sarcoma, the relation being about 3:4. In the first decade, however, the female sex distinctly predominates in frequency.

Osteogenic sarcoma is primarily a disease of the young. The Registry material upon which the adjoining curve is based shows that while there is no age entirely

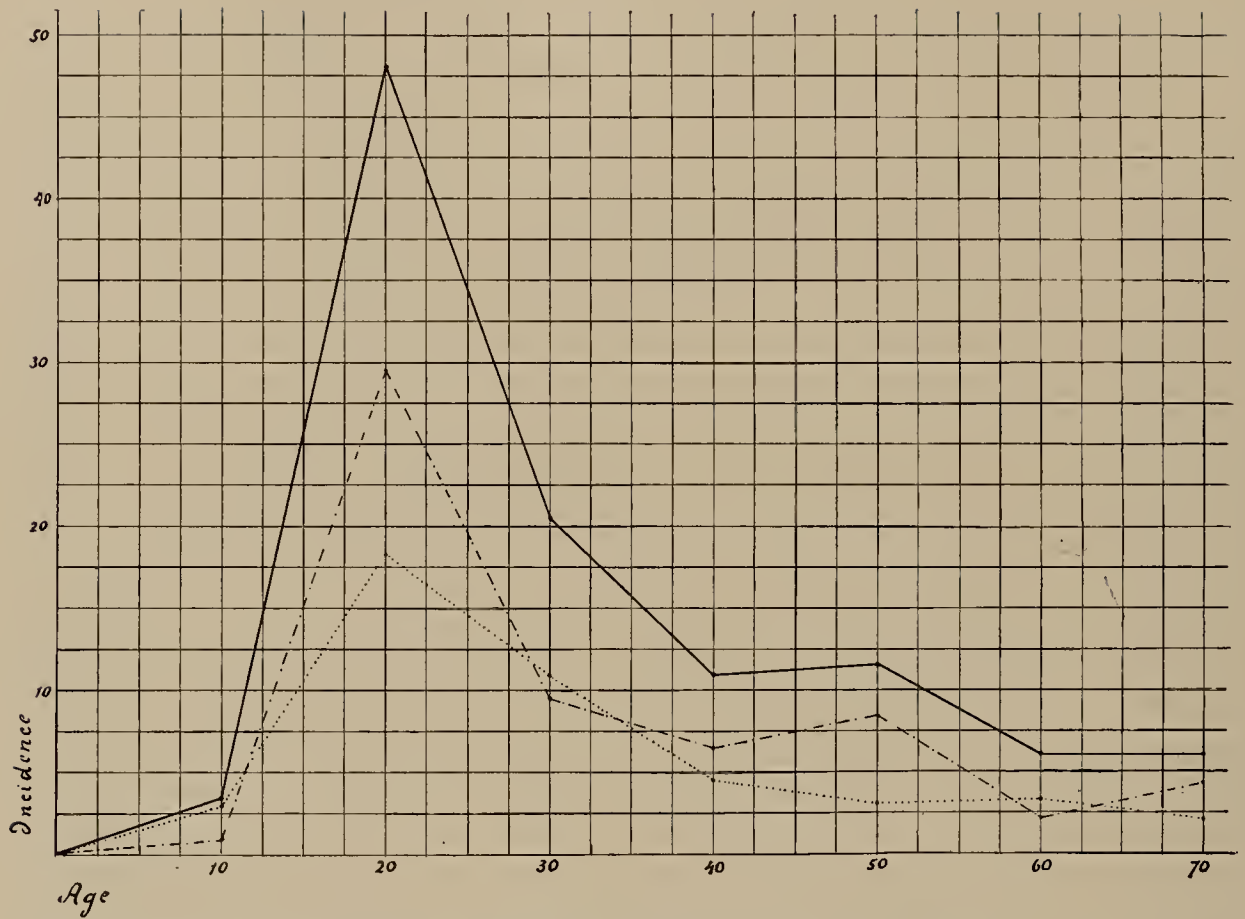


Fig. 40. Chart illustrating the incidence of osteogenic sarcoma in relation to age. Dotted line—females; broken line—males; heavy line—both sexes combined.

immune, the incidence of this tumor, however, predominates in the second decade of human life (Fig. 40). It is of the least frequency in the first decade, especially during the first few years of life. There is no authentic case on record of a congenital osteogenic sarcoma, the great majority of congenital sarcomata being located in the soft parts occasionally attached to the outer layer of the periosteum. The fact that osteogenic sarcoma develops most frequently during the period of the most energetic skeletal growth and the period of skeletal puberty has long been the basis for the inclusion theories of tumor origin and of theories of endocrine influences. The fact that the greatest frequency of osteogenic sarcoma is in the age of most active skeletal growth and development would certainly seem to indicate that energetic growth of the skeleton is one of the main factors in the etiology of these tumors.

While most bones of the skeleton may be the seat of osteogenic sarcoma they are, however, met especially frequently in the long bones. The metaphyses of the long bones are the seat of predilection of osteogenic sarcoma. This is especially marked in osteogenic sarcoma of the lower extremity which comprises about 72 per cent of all cases of osteogenic sarcoma; in 82 per cent of all osteogenic sarcomata of the lower extremity the tumor affects the region about the knee whether

it be the femur or the tibia. The relative frequency of osteogenic sarcoma in the upper and lower extremity may be expressed by the ratio 2:11; the tumors of the upper extremity comprising about 10.5 per cent of all cases of osteogenic sarcoma, and the relation between the extremities on the right and left side by the ratio 5:4. The individual bones of the skeleton with the highest frequency of involvement are the femur, tibia, humerus, all bones of the pelvis combined, the fibula, the bones of the shoulder girdle, the ulna, the bones of the hands and feet (exclusive of the phalanges of fingers and toes), the ribs, the skull, the jaws and the vertebræ. While the lower end of the radius is a common seat of giant cell tumor no authentic case of osteogenic sarcoma of this bone is known to the Registry, only two doubtful cases of osteogenic sarcoma having been recorded. The same is true of the lower end of the tibia, an homologous bone.

The bone most frequently involved in osteogenic sarcoma, the femur with its 52 per cent of all cases, has its seat of predilection in the lower metaphysis and in 82 per cent of all cases in the femur the tumor is situated in this region. The remaining 18 per cent are distributed in the shaft, about the great trochanter and in the neck. It is important to remember that about 9 per cent of all cases in the femur are located in the shaft of the bone without any gross involvement of either end. This is especially interesting since it is usually considered that an involvement of the shaft is pathognomonic of Ewing's sarcoma, and in several of the cases of involvement of the shaft in the Registry material this diagnosis has actually been suggested on account of this situation of the tumor. The features of this variety of osteogenic sarcoma will be pointed out more explicitly in the following chapter. The next seat in freqeuncy in the femur is the region about the great trochanter. Osteogenic sarcomata here are marked by the prevalence of cartilage. Degenerative changes frequently lead to cyst formation in these tumors. Occasionally the tumor appears to be attached to the trochanter by a well defined pedicle. The neck of the femur and the region close to the head are the seats of least frequency.

The second most frequently involved bone, the tibia, averages about 20 per cent of all cases. About 90 per cent of all cases situated in the tibia involve the region about the upper end of the bone. It is interesting to note that here the tumor is seen mostly on the internal aspect of the bone and very rarely on the lateral aspect. The remaining cases of osteogenic sarcoma are situated all along the bone except at the lower end.

The humerus carries about 9 per cent of all cases of osteogenic sarcoma, the majority being found in the upper third of the bone, very frequently about the insertion of the deltoid, while an osteogenic sarcoma below the deltoid tubercle is a curiosity. In the pelvis with its 5 per cent of all cases of osteogenic sarcoma the tumors are most frequently situated in the ilium, usually about the crest; sometimes they are found in the os ischium and rarely in the pubis. It is of

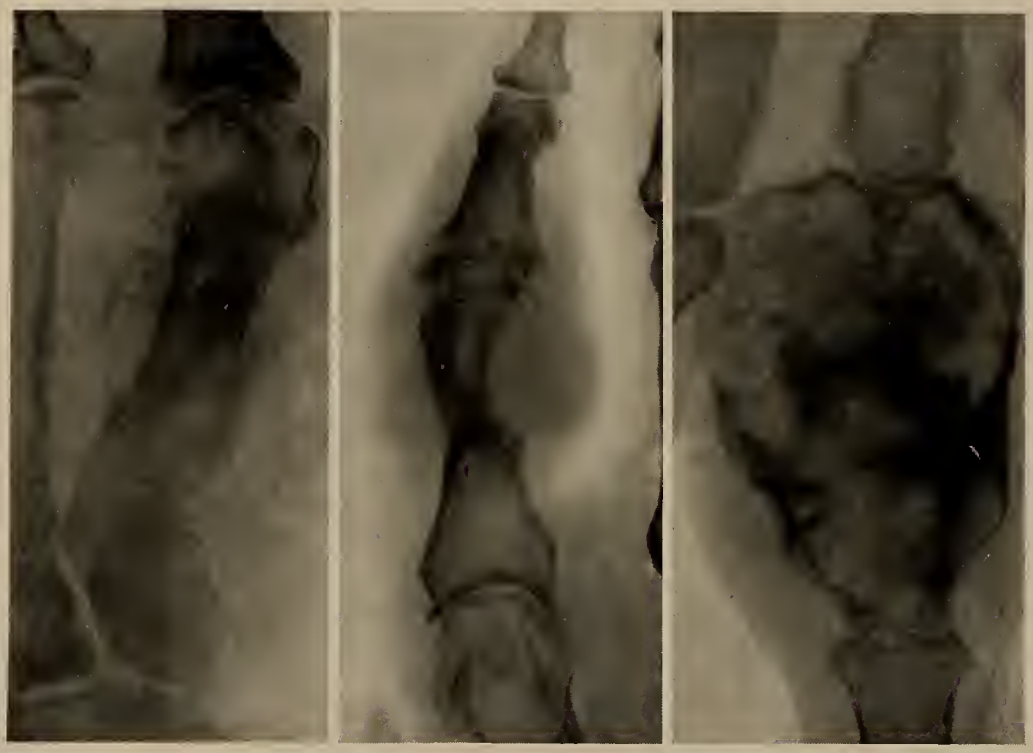


Plate 8. Roentgenograms showing (1, left) osteogenic sarcoma in a young woman; (2, center) solitary gout nodule which simulates an extraperiosteal sarcoma with pressure absorption of bone; and (3, right) enchondroma.

interest that the tuber ischii which is under frequent physiological stress is an uncommon seat of osteogenic sarcoma. The fibula is usually involved at its upper end; localization of an osteogenic sarcoma in the lower end of the fibula is rare. Of the bones of the shoulder girdle, the scapula is the seat of predilection, especially about the glenoid fossa. The ulna is usually affected at its proximal end, no case of osteogenic sarcoma in the distal end having been registered. Only the large bones of the feet are occasionally affected by osteogenic sarcoma; the phalanges of the fingers and toes are free from true osteogenic sarcoma (Plate 8). In fact no case of metastases from an osteogenic sarcoma of the phalanges is known. The skull is affected by osteogenic sarcoma mostly in children. An involvement of the lower jaw is more frequent than that of the upper. The vertebræ are very rarely the seat of an osteogenic sarcoma. An osteogenic sarcoma of the patella has never been registered.

The fact that a great majority of osteogenic sarcomata are found in the bones of the lower extremity led to a hypothesis that physiological stress and strain are in some way a predisposing factor in the etiology of osteogenic sarcoma. While it is true that the lower extremity is under incomparably higher stress and strain than the upper extremity, it cannot be denied that the spine far exceeds the lower extremity in this respect, yet osteogenic sarcoma of the spine is not common. On the other hand the localization of most osteogenic sarcomata about the knee, which is always exposed to trauma, suggests that trauma is a definite etiological

factor in osteogenic sarcoma. It has been mentioned above that the fact that the majority of osteogenic sarcomata occur in the young suggests that energetic skeletal growth plays a certain rôle in the etiology of osteogenic sarcoma. This suggestion is well in accord with the fact that the lower epiphyseal end of the femur and the upper epiphyseal end of the tibia are the last to ossify in the human being, remaining in the growing age until the first years of the third decade.

Osteogenic sarcoma is a solitary disease. In the literature where, under the heading of "bone sarcoma," are embraced together with osteogenic sarcoma also Ewing's sarcoma and myeloma, multiple bone sarcoma is frequently mentioned. It is of course not uncommon to find a multiple Ewing's sarcoma. In myeloma multiplicity is the rule. That myeloma has frequently been described as multiple "bone sarcoma" may be suspected from the fact that most reported multiple bone sarcomata were medullary in location. It would not be surprising if under certain conditions favorable for osteogenic sarcoma a patient should develop simultaneously more than one lesion; yet multiple cases are not common. It is impossible to decide whether a rare multiple osteogenic sarcoma is such from the start or whether one tumor is the primary growth and the others are of metastatic origin.

Sometimes an osteogenic sarcoma is superimposed on multiple chondral exostoses, in which case multiple osteogenic sarcomata may be encountered. Multiple lesions are also known to occur in patients with Paget's disease (osteitis deformans). Such cases often pass as metastatic from a single primary osteogenic sarcoma. Codman pointed out the fact that because most cases of osteogenic sarcoma occur under the age of 50 and most instances of Paget's disease are recognized over the age of 50 the presence of an osteogenic sarcoma in later life is almost presumptive of Paget's disease. The Registry material shows that in about 5 per cent of all cases of osteogenic sarcoma the tumor arises in Paget's disease. Codman believes that about 14 per cent of all cases of Paget's disease succumb to osteogenic sarcoma. It has been suggested that osteogenic sarcomata occurring in Paget's disease be separated as a definite entity. There is, however, no clinical evidence to support such a separation. As in most cases of osteogenic sarcoma, the etiological factors of osteogenic sarcoma in Paget's disease probably may be explained by local loss of growth restraint (repair restraint). Such a local loss of growth restraint when repair is called for has serious consequences in Paget's disease with its apparently constitutional weakness of general growth restraint (Plate 9).

In the clinical history of a patient with a primary malignant bone tumor there are two features which attract the attention of the diagnostician. One of these elements is pain, which is the first symptom in a patient with an osteogenic sarcoma. It precedes the appearance of a tumefaction by an interval lasting a

Plate 9. Courtesy of Dr. Holmes, Massachusetts General Hospital. Osteogenic sarcoma in a man of 49, with Paget's disease. The patient sustained a fracture of the femoral neck. While immobilized in a hip splint, he developed an osteogenic sarcoma. Roentgenograms taken soon after the fracture and 3 and 5 months later.

few days, weeks, or months. This symptom is of such importance that severe persistent pain in a long bone of a young adult should cause a suspicion of sarcoma. Pain is due to the high sensitiveness of the periosteum which invariably becomes affected to a greater or lesser degree in malignant bone tumors. Sometimes, however, pain is not proportionate to the seriousness of the condition; all the patient experiences first is a tired feeling, some uncertainty of the muscles about the adjoining joint and hence limping. When the process encroaches upon the periosteum, pain appears. Pain is of a very severe, boring, excruciating or rheumatoid and gnawing character. The suffering is especially agonizing and unbearable during the night, waking the patient from sleep. In fact the sleepless nights are the main cause of the run-down general condition so frequently seen in patients with osteogenic sarcoma. In the early stages pain may be intermittent in character. Pain of a rather dull character comes on immediately after trauma, lasts one to two weeks, disappears and all that is left is perhaps a slight limp. Some time may pass and the pain reappears, but of a deep seated excruciating character. Occasionally a new trauma precedes the reappearance of pain. Intermittent pain, however, is more typical of a Ewing's sarcoma than of osteogenic sarcoma.

The best explanation of the cause of pain is pressure of the tumor mass from within the bone upon the periosteum. That tension of the periosteum, and not pressure upon nerves as suggested by others, seems to be the cause may be concluded from the fact that in far advanced osteogenic sarcoma after the periosteum is perforated by the growing tumor mass, pain may disappear; the patient is up and around until a pathological fracture or metastases oblige him to become bed ridden. Pain is also relieved by drawing up the leg so as to relax the muscles overlying the tense periosteum. The spectacular and almost immediate disappearance of pain after radiation could hardly be explained by relief of pressure upon nerves, but it is well in accord with the radical influence of radiation upon the rapidly growing tumor. There are other conditions of bone in which pain is of similar severity, e.g., acute osteomyelitis with an accumulation of pus between the cortex and the periosteum. The pressure of the pus under high tension upon the periosteum causes the pain, and drainage here immediately relieves it. Similar pain is observed in syphilitic periostitis and in sclerosing non-suppurative osteomyelitis—conditions which greatly affect the periosteum. The appearance of pain is not in any way to be identified with the onset of the tumor. The not infrequent short duration of life after the onset of pain is the best proof that the tumor was present long before, and only when the periosteum became distended to a certain point did the pain call the patient's attention to the condition.

Another important element in the clinical history is trauma. The question of the importance of trauma as a diagnostic point in "bone sarcoma" has been

debated for years. As our knowledge stands today, one may say that trauma is an unreliable element in the history of a patient with a primary malignant bone tumor, and this is as true of osteogenic sarcoma, as of Ewing's sarcoma. The fact that statistical data vary greatly in the estimation of trauma indicates that there must be important sources of error in such statistics. The main error is evidently the question about which an immense confusion exists: "What is to be considered a trauma?" Is not a sudden tension of a muscle upon the bone to which it is inserted also to be considered a trauma? In accordance with the answer to this question the frequency of trauma in the clinical history will obviously change. Another error is due to the fact that the history of trauma is purely subjective and is apt to lack in trustworthiness; it is an old inclination of a patient to connect up his suffering with some external fact as a cause. We all frequently suffer traumata which usually pass unnoticed, but in the exceptional case when a tumor develops, we recall the trauma history. In some cases a trauma is mentioned by the patient for purely mercenary reasons. There also can be no doubt that in many cases the quasi-responsible trauma was sustained after the actual onset of the tumor. This fact is not sufficiently realized even by the diagnostician; meanwhile the occurrence of pulmonary metastases and death after a very short clinical course, 2 to 3 months after the discovery of the tumor by the patient, strongly support the possibility that the trauma in the patient's history took place after the actual onset of the tumor.

While there can be no doubt that the old motto, "When there is no trauma there is no tumor" is obsolete and not in accord with actual facts, there is, however, strong evidence to support the view that in general trauma may lead to osteogenic sarcoma under certain predisposing conditions. It is probable that trauma is the exciting cause of all osteogenic sarcomata but it seems that the particular trauma associated with the onset by the patient is seldom a causal trauma. The strongest argument against the importance of trauma in primary malignant bone tumors is the fact that osteogenic sarcomata are rare after fractures. However, sarcoma in callus after fractures does occur, to be sure not as frequently as one might expect if this kind of trauma were important in the etiology of osteogenic sarcoma (Fig. 41). As a matter of fact, the character of trauma preceding osteogenic sarcoma is usually not a severe blow producing a fracture, but a more or less slight trauma of the contusion type, frequently forgotten by the patient until reminded of it by the appearance of pain. In this all sarcomata differ from carcinomata where not a single but a repeated, more chronic trauma is important. Slight repeated traumatizing, however, is not infrequent in the histories of cases of osteogenic sarcoma. The trauma here is of a chronic irritative type, one which can hardly be qualified as a trauma in the usual sense of this word, for example an osteogenic sarcoma which arises in a bone scar of a cured osteomyelitis. Typical in this country are osteogenic

Fig. 41. Case 156. Osteogenic sarcoma in a boy 14 years old. The tumor arose at the point of a well united fracture which preceded the clinical onset of the tumor by 7 months.

sarcomata appearing after a sport trauma—football or baseball. In such cases the tumor is occasionally accompanied by myositis ossificans.

The question of how a trauma may lead to an osteogenic sarcoma furnishes ample material for speculation, most alluring being the theory of loss of repair restraint in the bone after the trauma. Important from a practical standpoint is the fact that the history of trauma is very frequently obtained from a patient with an osteogenic sarcoma and hence trauma plays a definite rôle as a diagnostic point in this disease. A history of trauma is more frequent in patients between the ages of 10 and 30, perhaps because they are more active and less careful than older people.

Of obvious importance is the time elapsing between the sustained trauma and the appearance of the tumor. In a large series of cases one finds the most discrepant intervals of time ranging between a few days and a year or more. The very short intervals of time are evidently of no diagnostic value; also the longer the intervals the less reliable is the history of the trauma. The most frequent interval is about one month between the time of the trauma and the appearance of pain or tumefaction. This interval is actually found in approximately one-third of all cases of osteogenic sarcoma.

Unlike carcinoma the general condition in malignant tumors of bone is generally good until the later stages of the disease. Of course night pains keep the patient in misery and may cause a rapid running down of his general condition, but as soon as this suffering is relieved spontaneously, by radiation, or amputation, the general condition of the patient is again satisfactory. Occasionally one observes a case of osteogenic sarcoma in which the temperature is high. The febrile stage usually lasts but a few days, disappears, and may recur at a later date. Such a febrile course, however, is more common in Ewing's sarcoma than in osteogenic sarcoma. When the patient enters the last stage—the generalization of the disease—a febrile stage is frequent, especially in the presence of pulmonary metastases with an accompanying consolidation of the entire lung. Along with the high temperature one sometimes finds hyperleucocytosis with a predominance of lymphocytes. Myelocytes are not a constant finding; when present they comprise about 3 to 5 per cent of the leucocytes. The clinical reaction of the patient to the disease in the terminal stage is also unlike carcinoma. Instead of cachexia, one encounters here a grave anæmia. The chalk pale patient has a characteristic haggard appearance, which when once seen is never forgotten. Occasionally the persistent lowering of the hæmoglobin, in spite of a good general condition of the patient, is a sign of a generalization of the disease. When the tumor is infected after an exploration, the general condition of the patient rapidly changes for the worse and may be followed by an appearance reminding one of cachexia.

The reaction of the skin overlying the affected region is also unlike that which is usually observed in carcinoma. While in carcinoma the skin overlying the

tumor early becomes involved, in osteogenic sarcoma the skin is persistently stretched by the tumor, but not invaded by it. It preserves its mobility and natural color for a long time. However, frequently the temperature of the skin overlying the involved area is distinctly higher than that of the neighboring areas. Early, dilated veins become noticeable. These dilated blood channels in the pale white skin give a striking danger signal to the observer. The skin usually remains intact, and if no exploration is done, an ulceration of the skin is rare. Occasionally, however, the skin becomes œdematous; it is tense and glossy, the superficial veins are very large. When the tumor is far advanced and the thinned out skin looks inflamed due to a dilatation of the superficial veins it acquires a purplish tint which may be followed by extensive excoriation. Inflammation may even go on to ulceration although this is very uncommon. These changes in the skin are of little diagnostic importance because they are observed late in the course of the disease.

The shape, outlines, and the consistency of the tumor are well perceived through palpation, and it is important to repeat such examinations frequently. By palpation one may often outline the anatomic borders of the tumor with a surprising exactness. Repeated palpation before and after radiation may bring out even the slightest changes in the consistency, size, and shape of the tumor, frequently most significant in establishing the diagnosis. In tumors with a very thin periosteal investing capsule and cystic degeneration one may encounter crackling; it is, however, a very uncommon finding. In very vascular tumors a pulsation and bruit can be felt. In the following chapter this feature will be dealt with in greater detail. Palpation may sometimes discover to the patient tenderness of which he was unaware before, since tenderness may be present in the absence of pain. It goes without saying that only when the utmost caution is exercised in palpation is the latter permissible.

The size of an osteogenic sarcoma is variable. In general in these days large malignant bone tumors are less frequent than twenty-five years ago—the tumor is usually diagnosed much earlier. Much depends on the seat of the tumor. When in close proximity to important structures an increase in size of the tumor may affect them and in this way draw the patient's attention to the disease. Usually only the primarily benign but potentially malignant skeletal chondromata of long duration reach a large size, before they become actual osteogenic sarcomata. The rapid and extensive regressive changes in malignant bone tumors may considerably slow down the increase in the size of the tumor. It is unsafe to attempt to state the time of onset of the tumor from its size. The rapidity of growth and the increase in size depends greatly on the consistency of the tumor tissue; the firmer osteoblastic tumors are of more moderate dimensions than the soft encephaloid variety. As a rule after the tumor breaks through the bone and the investing periosteal capsule, its rate of growth markedly increases. During

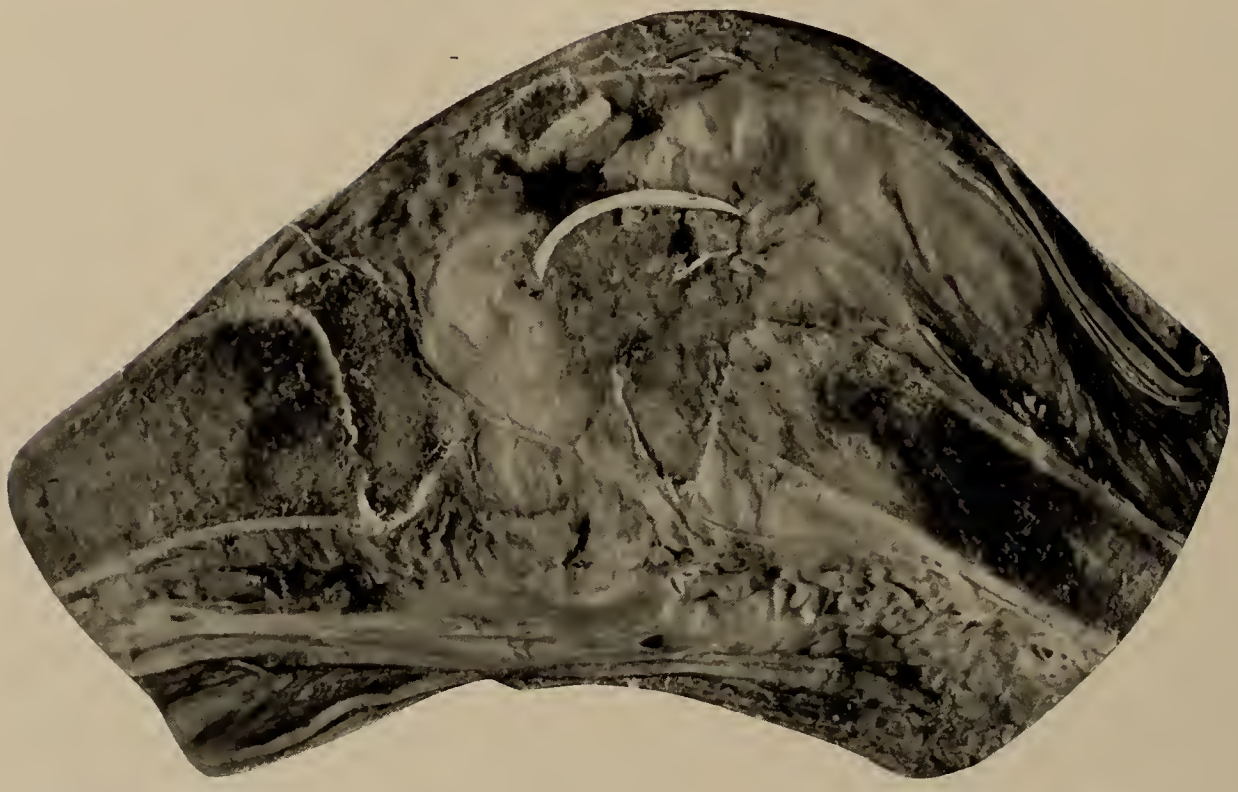


Fig. 42. Case 469. Osteogenic sarcoma in a boy 15 years old. Showing an extension of the tumor into the knee joint.

the course of an osteogenic sarcoma traumatism of any kind may lead to an acceleration of growth. By traumatism is meant here local direct as well as indirect general traumatism, for example hard physical labor, exercises of any kind, an exploratory incision or puncture of the tumor. After an exploratory incision the acceleration of growth is usually very acute. The fact that hard physical labor may have a sudden accelerating effect on the tumor may be important in the courts. The rate of tumor growth may be and probably always is accelerated by a pathological fracture through the involved area of bone.

In general, pathological fractures are not typical of osteogenic sarcomata. Usually tumefaction and pain are keeping the patient off his feet. They are more apt to occur in osteogenic sarcomata growing expansively in all directions in the involved bone, in the so-called central variety. The fracture follows a trifling trauma or force. It may also result entirely spontaneously and sometimes even without the patient's knowledge of it. Pathological fractures are usually transverse, not "green stick" but rather "rotten wood" fractures, although oblique pathological fractures do occur. Like pathological fractures in carcinomatous involvement healing of fractures here is not uncommon. Instead of callus it may unite by means of ossifying tumor tissue with a subsequent refracture when the new formed bone is destroyed by more cellular tumor tissue.

The reaction of the joint close to the involved bone end in malignant bone tumors is peculiar. It is interesting to note that a patient complains less of

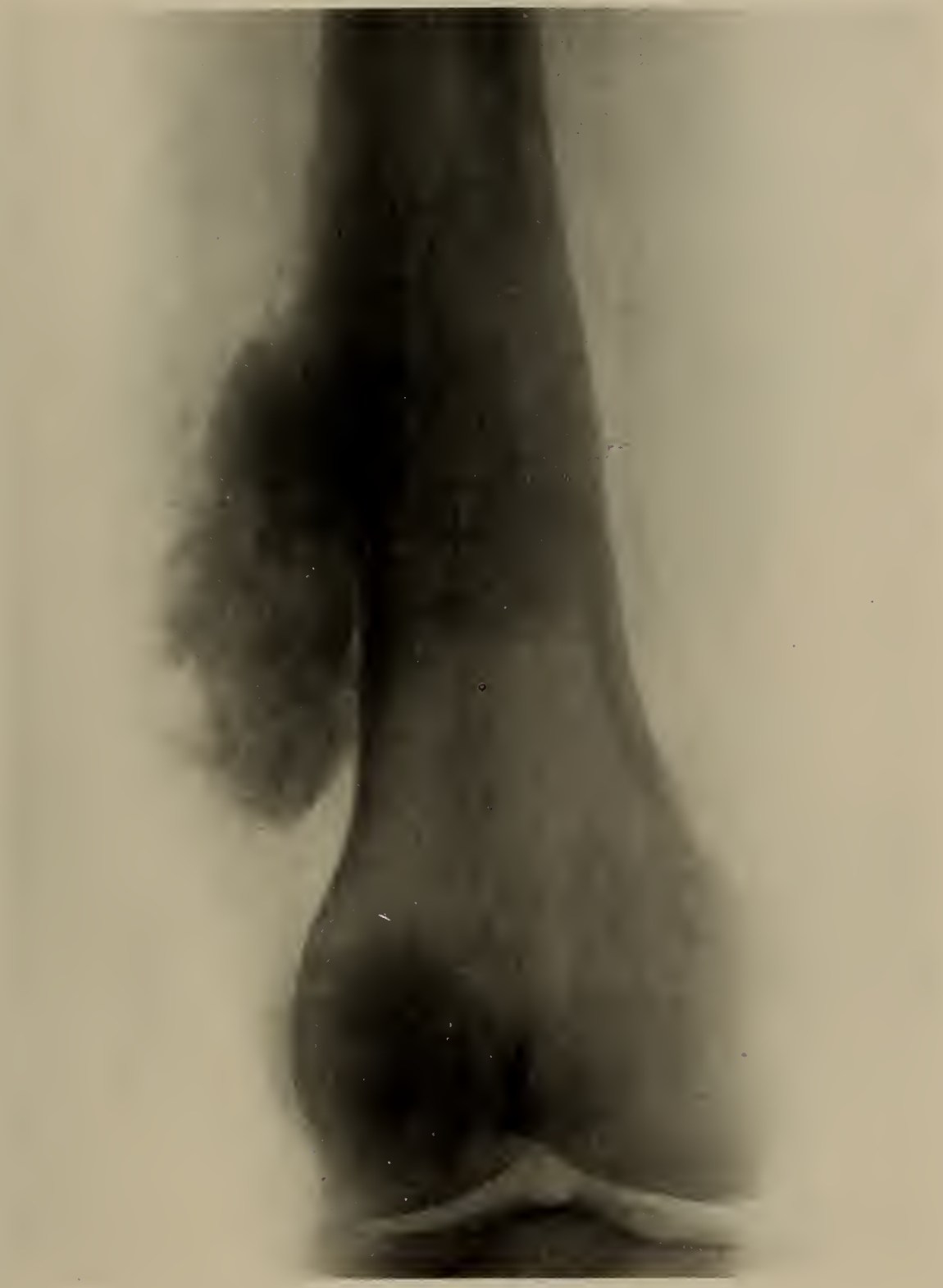


Fig. 43. Case 316. Skeletal chondroma in a man 58 years old. Onset in 1913. Local excisions of the tumor and recurrences in 1915, 1920, and 1923. The histology of the last recurrence showed distinct malignant features. The present roentgenogram was taken before the last operation.

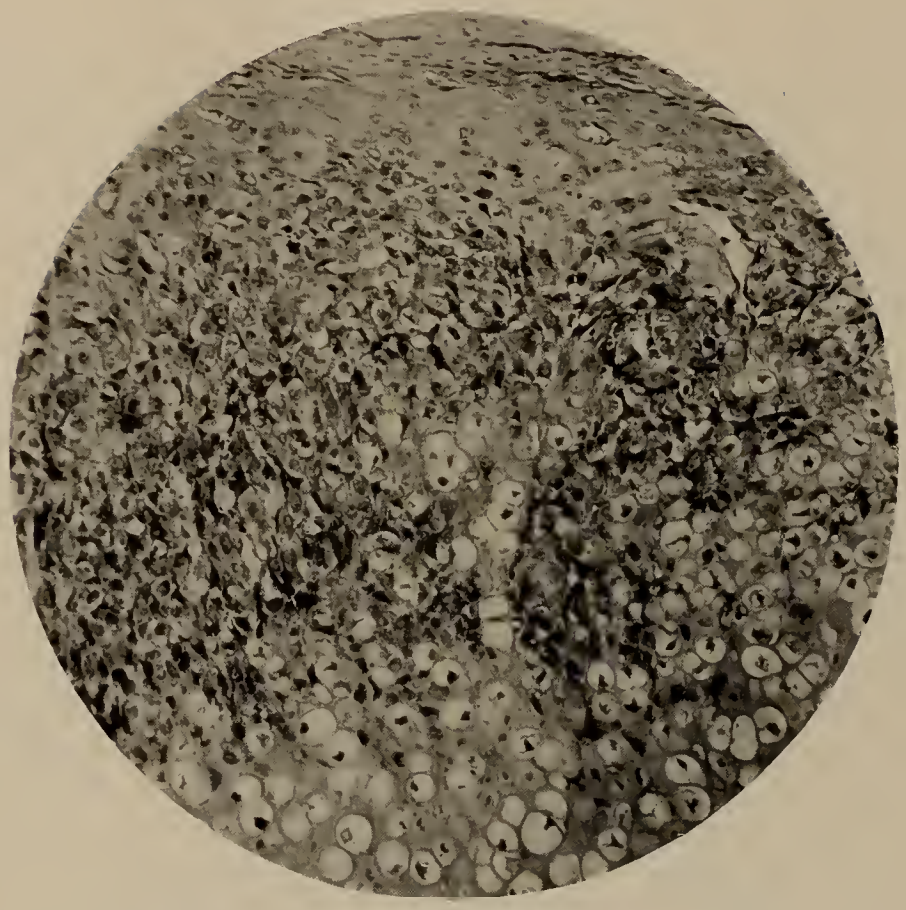


Fig. 44. Case 296. Same case as in Figures 45, 46, and 47. Skeletal chondroma. Showing a characteristic conglomeration of various typed cells beneath the fibrous capsule of the tumor.

articular pain in osteogenic sarcoma than in osteomyelitis. There may be initial soreness and perhaps an effusion into the joint cavity following trauma, but after the exudate absorbs, no articular discomfort is felt by the patient. Movements in the joint are free. In the far advanced stages of an osteogenic sarcoma there may follow a sarcomatous involvement of the neighboring joint. While involvements of the joint by extension from the tumor do not occur very frequently, they are, however, in my experience not uncommon. Because the articular cartilage is very resistant to sarcomatous involvement a penetration of the tumor into the joint does not take place through the articular cartilage (Fig. 42). It usually takes place following a pathological fracture through the involved end of the bone. Such joint involvement is more frequent in the adult than in the young, because of the completed fusion of the epiphysis; in the former the tumor frequently spreads directly in the epiphysis. When the joint is involved, it sometimes becomes distended with fluid and shows signs of fluctuation; this is, however, the exception and not the rule. Usually a fusiform enlargement of the joint slightly resembling a tuberculous arthritis is seen. Cases are even known of a diagnosis of tuberculosis on account of this similarity. On opening the joint the synovial membrane is found converted into a grayish red fungous tumor mass

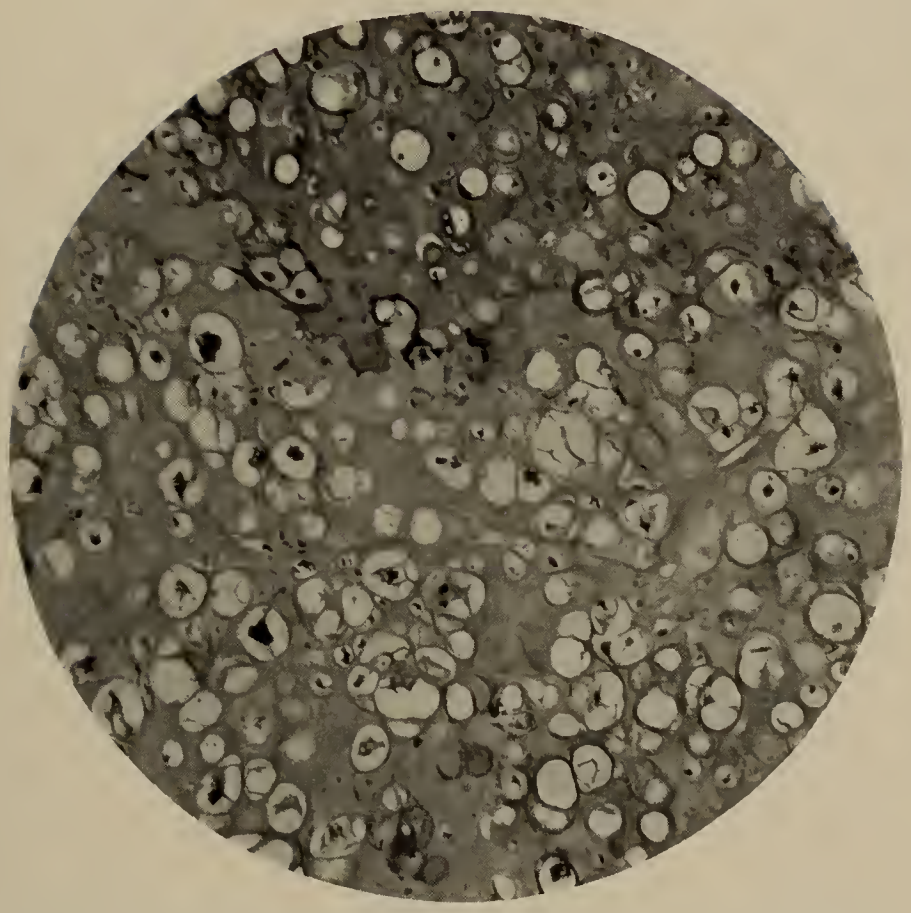


Fig. 45. Case 296. Compare with Figures 44, 46, and 47. Showing the preponderating structure of the tumor—atypical cartilage.

which is in direct communication with the extra-articular tumor. Sometimes the synovia is converted into a large nodular encephaloid mass. The knee is the joint most frequently involved; but other large joints may be affected in a similar way. There is some evidence that an osteogenic sarcoma after perforating into the joint may involve the adjoining normal bone from within the joint cavity. This is, however, very unusual.

One of the most constant manifestations of the clinical course of primary malignant bone tumors is generalization of the tumor, through metastatic dislodgment. In the literature one frequently finds most definite statements as to the frequency of metastases in malignant bone tumors. Similar statistical data are of no value unless they are based on cases histologically proved to be osteogenic sarcoma with the presence of metastases well established. In primary malignant bone tumors all similar statistical data are of relative importance because of the exceedingly grave prognosis of the disease; in only exceptional cases does the patient live more than five years, while in the majority of cases death is a result of generalization.

The idea that the blood stream is the only path of spreading of metastases in sarcoma does not hold true in malignant tumors of bone. The lymphatic system

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Fig. 46. Case 296. Compare with Figures 44, 45, 47. Focal hyalinization with ossification of the tumor.

occasionally plays a definite rôle in the transportation of tumor tissue in the organism. The importance of the blood channels in the generalization of the disease is, however, predominant. A perforation of the tumor mass into a blood channel is not uncommon, because of the intimate relation of tumor elements to the blood vessels as pointed out above. As a result of venous transportation of the tumor cells, pulmonary metastases are most frequent. From the lungs a dissemination may follow through the skeleton and parenchymatous organs. The perforation of a pulmonary metastatic mass into a bronchus with expectoration by the patient of fragments of seminecrotic tumor tissue has come under my personal observation. The incipient clinical signs of a pulmonary metastatic involvement may be the same as those in diffuse bronchitis. Sometimes a patch of pneumonia is diagnosed, the patient showing all the symptoms and signs of it—cough, dullness, fever, leucocytosis. In this connection it is important to remember that in cases in which, on physical examination, no involvement of the lung is found, a radiological examination may reveal early nodular metastases. Sometimes one is confronted with the necessity of differentiating in the roentgenogram between healed tuberculosis and tumor metastases. The best point of differentiation is the fact that in healed tuberculosis the nodules throw a deep, more or

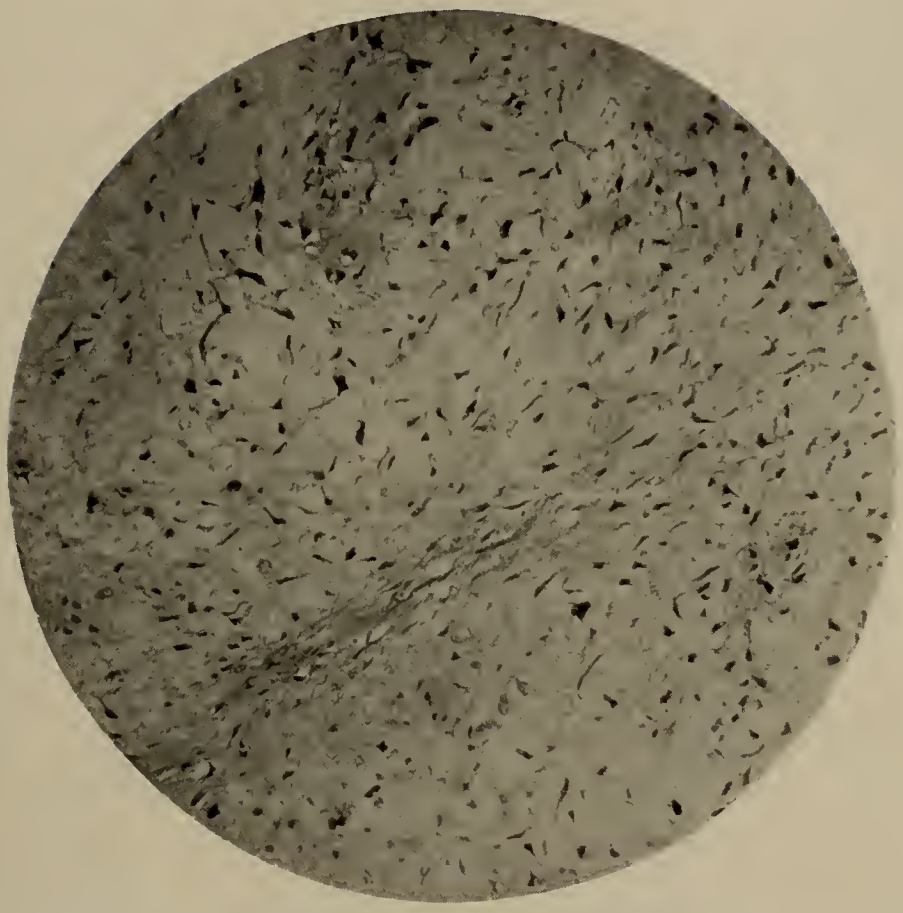


Fig. 47. Case 296. [Compare with Figures 44, 45, and 46. Showing an area of myxomatous degeneration of the tumor.

less rounded shadow the size of a large pea; this is due to the calcification taking place in healed tubercles. In early sarcomatous metastases no bone production is present usually and the shadow in the roentgenogram is faintly outlined. Negative physical and radiological findings do not rule out an early pulmonary involvement. Typical sarcomatous metastases are globular in shape, few in number, and large in size.

In the absence of pulmonary metastases, metastatic tumors have been found in other organs, especially in the bones. Some of these may be explained by retrograde transportation of the dislodged tumor elements, through veins, to their new location. In some the absence of pulmonary metastases is probably more apparent than real; it is also known that radiological evidence of pulmonary metastases may entirely disappear temporarily after radiation therapy.

Spreading of tumor metastases through lymphatics is infrequent. It is obvious that a metastatic involvement of regional lymph nodes in malignant bone tumors means more as an indication of generalization than in carcinoma. An occasional simple lymphadenitis in malignant bone tumors should be clearly distinguished from a metastatic involvement of the nodes. Such a lymphadenitis is usually found following an infection after ulceration of the tumor or after an exploratory

incision. However, an inflammatory reaction in the regional lymph nodes is also encountered when there is no ulceration present.

Naturally, a question arises as to the interval of time between the onset of osteogenic sarcoma and the appearance of metastases. No definite answers as to this question can be made; in certain cases pulmonary metastases and death have been known to take place two months after the clinical onset, in others metastases have not been discovered until years after the onset. Usually metastases develop during the first two years after the onset. Cases are known in which pulmonary metastases led to the discovery of the primary tumor. In this respect osteogenic sarcoma is like carcinoma—not infrequently extensive skeletal carcinosis may be the first indication of the presence elsewhere of a primary tumor.

Skeletal chondroma is related clinically to osteogenic sarcoma. This is a primarily benign tumor which is notoriously persistent, grows to a large size, tends to recur after incomplete surgical procedures and finally to metastasize. The most frequently given history is that for some cause a tumor developed. It reached a considerable size; it remained benign for years until some kind of trauma, accident or a surgical operation, led to a sudden increase in vitality, to a distinctly malignant change, and to metastases and death. Putting it in terms of the repair theory the trauma calls for a new attempt at repair in the tumor; but because growth restraint is low or entirely absent, as is suggested by the primary development of the tumor, a more malignant tumor develops. The long space of time before a sudden turn for the worse after the trauma is the prevailing feature of this type of tumor. At operation the tumor appears perhaps not to involve the cortex of the bone on top of which it is situated, a local excision is done, and a rapid recurrence follows. Because of recurrence repeated local operations are performed. These surgical operations are followed by an increase in the blood supply of the tumor and by a change to malignancy. Their metastases and final course are typical of osteogenic sarcoma. These tumors are usually located in the diaphysis near the epiphyseal end of the bone. Sometimes they are distinctly pedunculated, in which case they are of far better course and prognosis. Frequently, however, the pedunculation is more apparent than real. They may lie entirely beneath the periosteum, projecting externally and pushing outward the periosteum; they may simultaneously grow in the medullary cavity, distend the latter and become surrounded by a thin bony shell. When they extend far, they may prove malignant from pure mechanical factors. The most frequent location of these tumors is the lower end of the femur, about the popliteal space (Fig. 43). Here they may reach an enormous size without great discomfort to the patient. They are frequent about the hip joint, especially about the great trochanter. The insertion of the broad pedicle to the trochanter is noted. In this location the tumors often pass for fascia sarcoma. Similar tumors are known to occur also in the upper end of the humerus and in the neck

of the scapula, about the glenoid fossa. Occasional instances of this tumor occur in various other locations. The histological structure of skeletal chondroma is manifold; it frequently resembles an osteogenic sarcoma with a preponderance of a cartilaginous matrix (Figs. 44 to 47).

Diagnosis

There are few chapters in medicine where exact diagnosis is hampered by so many difficulties as in malignant bone tumors. The confusion in the nomenclature and classification together with the fact that commonly these tumors are seen only at one or another stage of development, and the peculiarly complicated reactive processes of bone which contribute to the wide variations in their histological structure render the primary malignant bone tumors a complex diagnostic problem. Here it is that a collective study of many individual cases may greatly clarify diagnostic points. A very valuable contribution on the diagnosis of osteogenic sarcoma is written by Codman.[1] The diagnosis of malignant tumors of bone rests upon a careful consideration of the findings accumulated from all three angles of study: the clinical, roentgenological, and pathological.

Occasionally the history and clinical picture of the condition will suffice to establish the diagnosis, without the necessity of roentgenological or microscopical study; not infrequently a roentgenogram is more decisive in the diagnosis than a number of microscopical sections, but it is not at all uncommon for a most careful scrutiny and perusal of all available clinical and laboratory methods to prove insufficient for establishing a diagnosis. In general it is fundamentally wrong to emphasize the importance over the others of any one of the three angles of study, clinical, roentgenological, or pathological.

The importance of the history and the clinical course of a tumor of bone from the diagnostic standpoint has already been pointed out. These data are especially valuable in the early stage of disease when no tumefaction can be demonstrated. It is in this early stage that the patient's complaints are usually diagnosed as articular rheumatism. Articular rheumatism is the *primum refugium* of the unscientific physician not only in malignant skeletal tumors but in various other pathological conditions of the skeleton. It is indeed surprising how frequently this diagnosis is made by the physician in the presence of symptoms which, if evaluated intelligently, would lead one away from this diagnosis. Freedom of movement of the joint is an important differentiating feature between articular rheumatism and osteomyelitis on one side and osteogenic sarcoma on the other. In the latter, complete or relative freedom of motion in the adjoining joint is the rule except in occasional, far advanced cases when a secondary sarcomatous involvement of the joint proper takes place. Repeated careful palpation will not infrequently lead to an early discovery of a tumefaction.

[1] Codman, E. A. Registry of bone sarcoma. Surg., Gynec. & Obst., 1926, xlii, 381.

A clinical finding which is frequently misinterpreted and therefore misleading in the diagnosis is pulsation of the tumor. Allusion is made here to pulsation resident within the tumor itself and not to pulsation transferred to it from contiguous arteries. The occasional observation of pulsation and bruit in bone tumors has led to the diagnosis of these tumors as aneurysm of bone. One of the causes of pulsation in the tumor is richness in blood supply. In cellular, rapidly growing tumors extensive regressive changes may be followed by a formation of blood cysts and spaces which may cause pulsation. However, in skeletal tumors these factors cannot explain pulsation satisfactorily. The difference in the pulsation of a soft tissue tumor and a skeletal tumor may be brought out by a compression of the afferent main artery when the compression is followed by the disappearance of pulsation in a soft tissue tumor but not the entire disappearance in a pulsating skeletal tumor. This is probably due to the fact that the bone-marrow is pulsating normally. Apparently the influx and reflux of blood in the wide-meshed and thin-walled abundant capillaries transmits the pulsation to the delicate and loose cellular tissue of the bone-marrow. Whatever the exact nature of this tumor pulsation may be, it is fully attested that no aneurysmatic skeletal tumors exist.

To read and interpret correctly a roentgenogram of a bone tumor is an art acquired only with wide experience, combined with a thorough knowledge of gross pathology. For this reason individual statistics showing the high or low percentage of cases diagnosed correctly from the roentgenogram are not of much importance. The tendency in vogue a decade ago to overestimate the importance of a roentgenogram in the diagnosis of a skeletal tumor has been followed lately by a swing toward underestimating its importance. This swing has taken place because of the frequent errors in the diagnosis if one depends on the roentgenogram alone. The numerous difficulties which render a roentgenological study of an osteogenic sarcoma a complex problem are evident. The roentgenological features of an osteogenic sarcoma greatly depend upon the stage of the clinical course and upon the structural peculiarities in the tumor. The extensiveness of the tumor whether more medullary or cortical, the histological structure of the tumor, the destructive and proliferative bone reaction, the regressive changes with occasional subsequent formation of blood spaces and sinuses and cysts—these are just a few of the factors strongly influencing and complicating the roentgenological features of osteogenic sarcoma.

The great difficulties connected with the establishment of a correct diagnosis of osteogenic sarcoma from the roentgenogram, however, do not reduce its proper importance as a diagnostic aid. With our growing knowledge of this subject it is easy to see that in the future we shall have to make more extensive use of the roentgenological features of bone tumors for diagnostic purposes. From a study of the extensive material of the Registry one arrives at the conclusion that roentgenology is not sufficiently appreciated by the average physician in dealing with

bone tumors and too few roentgenograms are being taken. Not only among general practitioners and occasional surgeons but also in special surgical institutions the fact is not sufficiently realized that a roentgenogram is to be looked at as a method, harmless for the patient and most important for the physician, of frequent re-examination of a patient with a skeletal malignant tumor. In the presence of a suspected skeletal malignancy most of the bones of the skeleton should be examined roentgenologically. This is the only way to reduce *ad minimum* the number of cases in which a multiple tumor is to be mistaken for a solitary one. From the numerous unsatisfactory roentgenograms one sees how frequently most important technical points of roentgenology are not appreciated and are neglected. Probably the best films are secured with no screens and with long exposure. Because distortion is increased toward the margin of a film no details can be seen at the marginal zone of a large film which would warrant a diagnosis of importance. Such roentgenograms, to present details, must be taken with the proper tube and film—fine focused tube, small cone, small film. The Bucky diaphragm requires especial care since the lead striations showing up on a film in faulty technique cloud the picture and frequently prevent the correct analysis of it. Films at the usual two planes intersecting at right angles are indispensable here. Since a certain amount of detail is constantly lost in a print it is obvious that when important conclusions are to be drawn from the roentgenogram all studies ought to be made from the negative.

Speaking in general terms one may mention the following features of an osteogenic sarcoma which are frequently sufficient to differentiate it from other skeletal lesions. One of these features is the common absence of a definitely limited outline of the sarcomatous tumor. Since osteogenic sarcoma frequently spreads and for some time remains beneath its periosteal investing capsule a spindle shape of the tumor is common. In rapidly growing tumors the fusiform swelling is ossified only at the ends where the periosteal reaction succeeded in producing a bone shell in the investing capsule. In such cases the tumor will be revealed in the roentgenogram by a wedge shaped osteophyte at each pole of the spindle, springing from the periosteum and slowly fading away in the unossified soft tumor. The wedge shaped osteophyte is frequently spoken of as lipping of the periosteum. However, no one of the three mentioned features is absolute proof of malignancy, non-sarcomatous skeletal lesions sometimes presenting one or another of these features. This makes the diagnostic value of these points of only relative importance. In the presence of strong clinical evidence of malignancy roentgenological findings negative for malignancy are of little value.

The roentgenological appearance of an osteogenic sarcoma depends greatly upon the character of the bone reaction of the tumor and its degree of differentiation. It is chiefly roentgenologically that osteogenic sarcomata may be divided into osteoblastic and osteolytic. Taking general features, two types of ossification

can be distinguished in osteogenic sarcoma. One is the structural dense bone which springs from or is attached to the involved old bone, appearing on the roentgenogram as spicules radiating from the bone or as thin layers of osseous tissue parallel to the bone. The other type of ossification is structureless. The roentgen-ray shadow is spotted due to the presence of opaque areas in the tumor. It is commonly believed by radiologists that islands of opacity in a large tumor indicate that it is benign, since these areas are thought to be due to calcification and not true ossification. This belief is erroneous; frequently irregular so-called low grade bone will cast such a spotted, speckled shadow.

The most widely known roentgen-ray appearance of an osteogenic sarcoma is the so-called fan-like, sun-ray structure. The histology of these spicules and the probable cause of this arrangement has been mentioned above. This sun-ray arrangement of the new formed bone has for long been thought absolutely pathognomonic of osteogenic sarcoma. A similar arrangement in other skeletal lesions —in chronic inflammatory processes—is known to occur. Only in 18 per cent of the cases of osteogenic sarcoma of the Registry material a sun-ray arrangement of the new formed bone is seen. On the other hand cases of osteogenic sarcoma have been observed in which the arrangement of the new formed bone was in longitudinal striations. Such longitudinal striations, rare in osteogenic sarcoma, are usually observed in cases with a wide involvement of the shaft of the bone, similar in situation to that usual in Ewing's sarcoma.

There has been expressed an opinion in the literature that the arrangement of new formed bone in an ossifying tumor is chiefly dependent on its amount, on the rate of formation, and not on the nature of the cells from which it springs. These authors maintain that if the rate of growth of the tumor is slow and ossification tendencies are great, the newly formed bone is usually deposited with a spongy arrangement and not in radiating spicules. These statements seem purely contentious and unavailing in the face of the evidence accumulated from an examination of the Registry material with this point in view. If all cases of osteogenic sarcoma of the Registry are divided in two groups, in one group all cases before the twentieth year of age and in the other all patients above twenty years old; the first group—when the growth of the skeleton is at its height—shows that bone production is predominant in 86 per cent of all cases, while in the second group—when the skeletal growth has been completed—production of bone prevails in only 62 per cent. But the arrangement of the new formed bone in radiating spicules is also much more frequently observed in the first than in the second group. In the first group it is observed in 28 per cent of all cases and in 33 per cent of the cases of this group with bone production, while in the second group it is present in 8 per cent of all cases and in 13 per cent of the cases of this group with bone production. These figures speak against the suppositions mentioned above that the frequency of the arrangement of the formed bone in spicules is in inverse

ratio to the amount of the new formed bone. It is evident that the age of the patient exerts a great influence upon the amount of new formed bone as well as on the arrangement of the bone.

In the osteolytic osteogenic sarcomata, the periosteal reaction together with the lipping of the periosteum may appear very late; therefore waiting for the typical lipping for the diagnosis is not recommended. In the usual osteolytic osteogenic sarcoma the roentgenogram shows, at first, expansion of the involved bone to a small degree. Then the bone shadow becomes spotted because of areas of bone destruction. In the print such a roentgenogram looks as if one erased the bone in spots (Fig. 48). Such cases resemble metastatic skeletal tumors with a predominance of destruction. It is in such cases that a pathological fracture is a more or less frequent complication. In rare instances of osteogenic sarcoma the destruction of the bone is more circumscribed and limited to a smaller area; this is usually observed in tumors located in or about the epiphysis (Plate 10).

A large expansion of the involved shaft is rather an exception and not the rule in osteogenic sarcoma. The old shaft is usually seen in osteogenic sarcoma passing not expanded through the fusiform tumor mass. The sclerosed shaft may even appear in the roentgenogram to be shrunken. That there are exceptions when the bone is first expanded and then destroyed has been mentioned above. Such a course is usually observed in cases with a wide

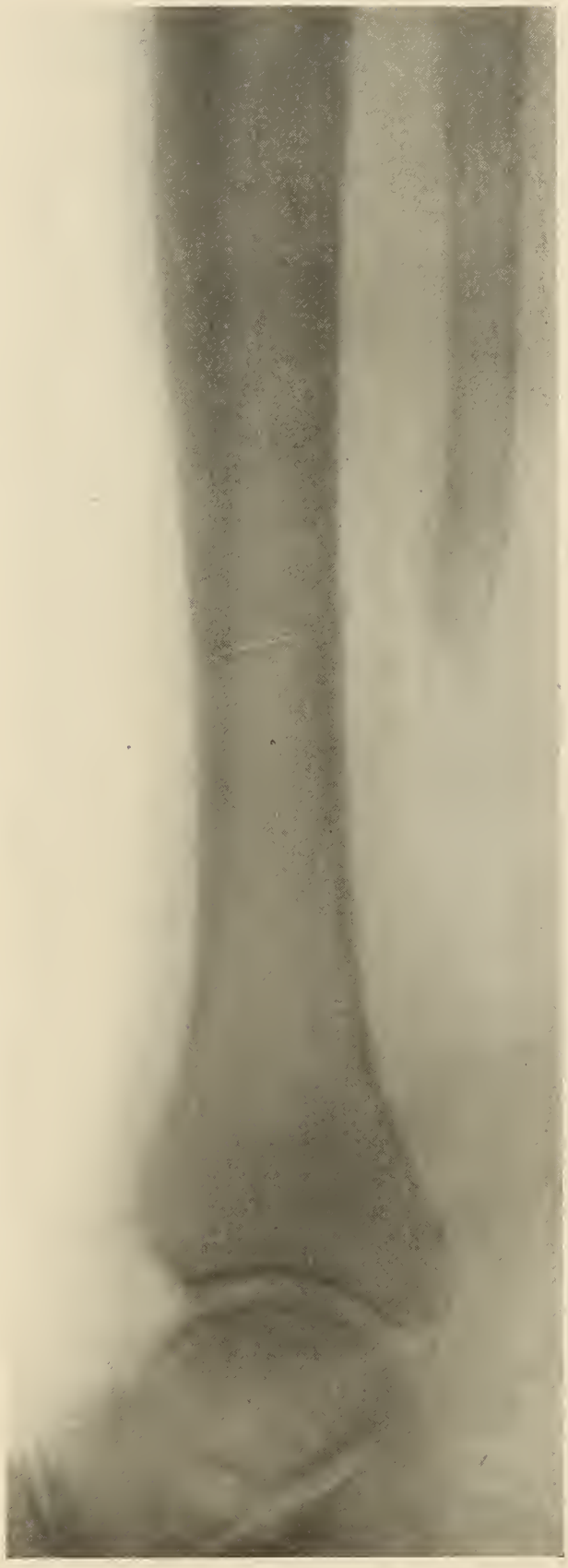


Fig. 48. Case 129. Osteogenic sarcoma in a woman 55 years old. Osteolytic variety. Death 1 year after onset.

Plate 10. Case 473. Osteogenic sarcoma in a boy 11 years old. Osteolytic variety which is uncommon in the young. The tumor was curetted because of an erroneous diagnosis of giant cell tumor. Death 10 months after the onset.

involvement of the shaft of the bone, slightly resembling Ewing's sarcoma roentgenologically. The shaft of a bone surrounded by an osteogenic sarcoma and appearing normal in the roentgenogram is not to be considered free of involvement; a tumor may show up well around a bone which casts a normal appearing shadow despite an extensive involvement of the haversian system and medullary cavity. For the same reason to attempt to define the extent of involvement by roentgenological evidence alone is hazardous in surgical therapeutic considerations.

Important for the diagnosis as some roentgenological features of osteogenic sarcoma may be, it would be misleading to consider them as absolutely pathognomonic. Setting up rules in the roentgenology of bone tumors will only contribute greatly to the discredit of roentgenography as a leading diagnostic method in skeletal oncology. Most of the roentgenological diagnostic points enumerated

Fig. 49. Case 222. A benign osteogenic tumor in a man 22 years old. Onset in 1910. Local excision in 1914. The patient was well in 1923. Note the sharp outline of the base of the tumor, the uniform density of the tumor and its jagged, velvet-like dome.

above may become worthless in an attempt to differentiate from osteogenic sarcoma a skeletal lesion with the same given roentgenological feature. For these reasons it is important to review here the skeletal lesions most frequently confused roentgenologically with osteogenic sarcoma, and to stress the chief

Plate 11. Case 216. See Figure 19. Osteogenic sarcoma in a woman 27 years old. Notice the speckled appearance of the tumor in the roentgenogram. The tumor cells are highly differentiated; bone with excessive cartilage formation make up the bulk of the tumor.

differentiating points. The differentiation from osteogenic sarcoma of other primary malignant skeletal tumors as well as giant cell tumors will be dealt with in the corresponding chapters.

As was mentioned, one of the most important roentgenological features of osteogenic sarcoma is that it is rarely definitely limited. However much depends on the stage in which the osteogenic sarcoma is seen; not infrequently after intensive radiation the tumor commences to cast a quite sharply limited shadow. In these instances the roentgenogram may not be inconsistent with the appearance of a benign osteogenic tumor. However the uniform density of the benign tumor, with the dome of the tumor jagged, velvety like, because of its cartilaginous covering, will frequently help to decide the diagnosis. In a benign osteogenic tumor there will be in most cases a sharp outline of the tumor toward the bone and the surrounding soft tissues (Fig. 49). A benign osteogenic tumor has cartilage on the external surface only, in imitation of the articular ends of long bones; cartilage dispersed throughout the tumor mass speaks for osteogenic sarcoma and against benign osteogenic tumor. Lipping of the periosteum is absent in a benign osteogenic tumor. It is also very unusual for a benign tumor to present the spindle form typical of osteogenic sarcoma. There is, however, a condition which, although rare, may puzzle the diagnostician because of the spindle shaped shadow of the roentgenogram even with presence of lipping of the periosteum. It is a subperiosteal hæmorrhage in hæmophilia. The periosteum is stripped away by the extravasation, the whole process forming a fusiform swelling. The pressure of the blood upon the bone may be so high as to cause an erosion of the cortex. Such cases have been reported in the literature. Similar confusion may be caused by Moeller-Barlow's disease with the only difference that there the hæmorrhages are usually limited to the diaphyses of the long bones.

That the sun-ray arrangement of the new formed bone was present in the Registry material in only about 18 per cent of cases was mentioned above; there was also indicated that such a radiation of the new formed bone lamellæ may be seen occasionally in chronic inflammatory conditions of the skeleton. Even less dependable for the diagnosis of osteogenic sarcoma is the longitudinal striation of the new formed bone, when the old cortex seems to be frayed longitudinally. It is not unusual to find such a structure in periostitis whether traumatic or inflammatory. In traumatic periostitis, however, the outline of the shaft remains distinctly limited and the cortex uneroded by the exostoses. It is uncommon for traumatic periostitis to surround the whole periphery of the bone as does osteogenic sarcoma. That, as a result of traumatic periostitis, large tumors may appear is known from the literature. In connection with this one has to consider also myositis ossificans, which is especially confusing when accompanying an osteogenic sarcoma as it is occasionally observed in osteogenic sarcoma after sport injuries.

Plate 12. Case 533. Multiple intra-osteal chondromata in a girl 8 years old. The entire skeleton was involved. The histology was inconclusive. Heavy radiation led to local improvement.

One can be more baffled in diagnosing a skeletal lesion by the possibility of a periosteal or cortical gumma than by periostitis. The similarity between syphilitic skeletal lesions especially gummata, and osteogenic sarcomata may be so great that despite all precautions many experienced diagnosticians have met with errors at some time or other. This is sufficient reason why one should refrain in doubtful cases from attempting a diagnosis before the result of a blood Wassermann reaction or even a provocative reaction is known. There are, however, some points which may help one in differentiating between syphilitic skeletal lesions and osteogenic sarcoma. A gumma is growing less rapidly than a sarcomatous tumor; the regressive changes in gumma take place much earlier than in osteogenic sarcoma. The extensive destruction of bone by gumma in the presence of a small sized tumor and the common absence of the periosteal spindle speak well for gumma and against osteogenic sarcoma.

When the new formed bone is present as foci throughout the tumor mass the roentgenogram is characterized by a spotted appearance. A picture similar to that is observed in skeletal chondroma. The calcified foci disseminated throughout the cartilaginous tumor cause a characteristic speckled mottled appearance with the individual spots sprinkled about (Plate 11). The differentiation in the roentgenogram between skeletal chondroma and osteogenic sarcoma is feasible. The sharply outlined pedunculated base of the tumors springing from a bone without any demonstrable pathological changes and the absence of the periosteal spindle will frequently suffice to establish the correct diagnosis. More difficulties may be encountered in intra-osteal and multiple chondromata. They are frequently seen in the upper portion of the femur, about the great trochanter. In such instances the question of differentiating between these tumors and an osteolytic osteogenic sarcoma may arise (Plate 12). At variance with osteolytic osteogenic sarcoma is the thinning of the cortex in central chondromata, and also the honeycombed structure with the thin, well defined bony septa traversing in the roentgenogram the defect in the osseous tissue of the bone. Not infrequently a question arises of differentiation between an osteolytic osteogenic sarcoma and skeletal carcinomatous metastases. This is hardly possible from the roentgenogram alone, but the presence of lipping and an unexpanded shaft speak for sarcoma.

More uncommon is the necessity of differentiating between osteogenic sarcoma and a bone cyst. Such a differentiation meets with fewer difficulties. This is especially true in more advanced cases. The clinical similarity between a bone cyst and osteogenic sarcoma may be great. The rheumatoid night pains, tenderness, although less marked than in osteogenic sarcoma, and pathological fracture all may be present with a bone cyst. Thus the clinical picture of a bone cyst as it usually appears in the young greatly resembles osteogenic sarcoma and the clinical examination alone will be insufficient for an accurate diagnosis. A

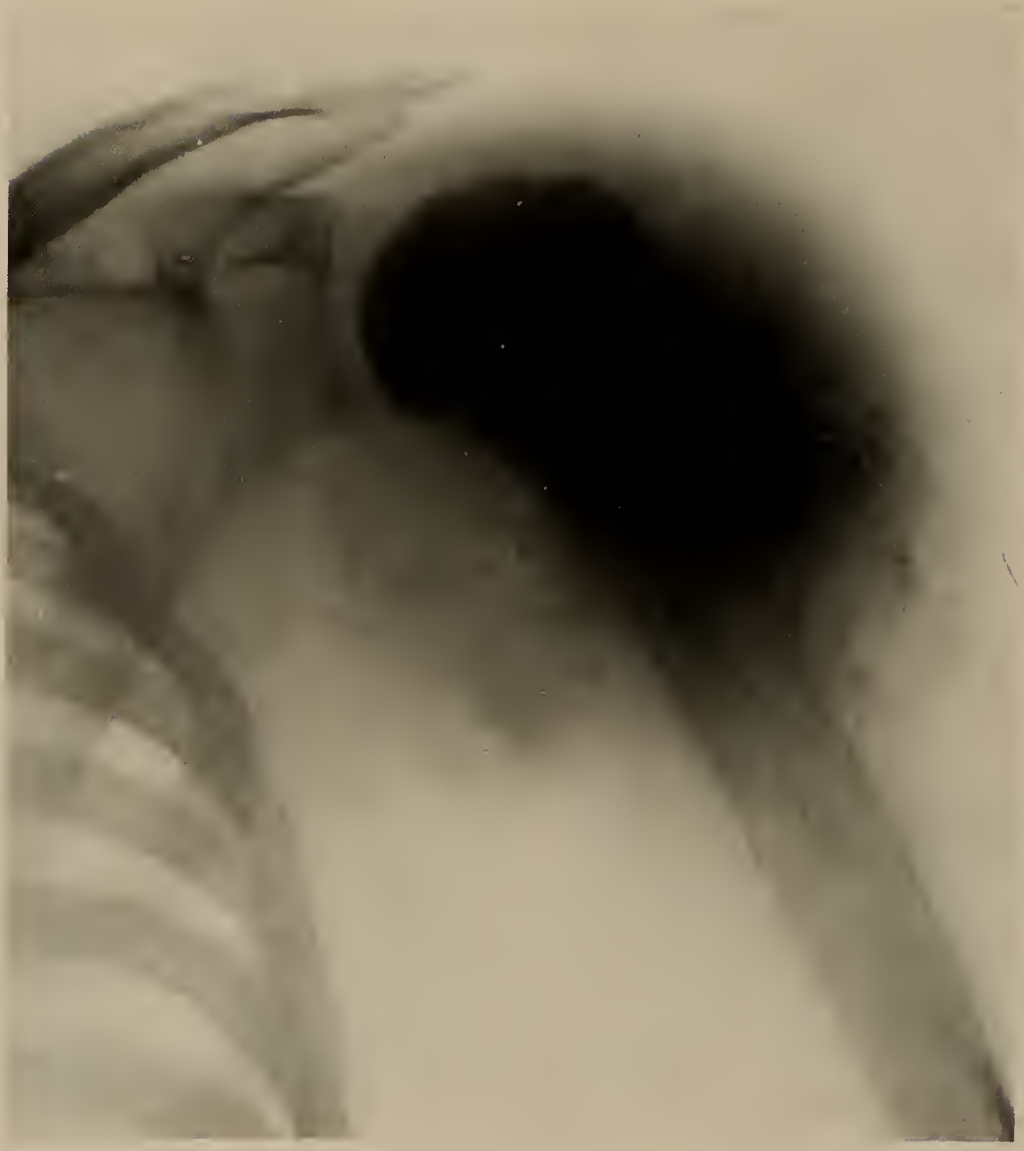


Fig. 50. Case 371. Osteogenic sarcoma in a boy 16 years old. Typical as to location and radiological appearance. The roentgenogram was taken 2 months after the onset at which time pulmonary metastases were demonstrated. Death 7 months after the onset.

roentgenogram will be almost indispensable although in the early stages a roentgenogram may be of no avail in the attempt to differentiate the lesion from an osteogenic sarcoma. The chief sign of a bone cyst is that it is always intra-osteal, i.e., central. Its presence usually leads to some expansion of the shaft; the cortex may become very thin but it is uncommon to have a perforation of the bone shell. Theoretically there is no reason why an actively enlarging bone cyst should be unable to perforate the cortex, but clinically such a perforation is a curiosity, probably because a pathological fracture interrupts the activity of the cyst when the latter is little short of a cortical perforation. When the cyst is located in the diaphysis it is usually ovoid in shape while the roentgenogram of a cyst in the ends of the bone may show a trabeculation similar to giant cell tumor.

Fig. 51. Personal observation; case not registered. Osteogenic sarcoma in a girl 8 years old. Death 9 months after the onset. The shaft of the bone is seen passing through the tumor which surrounds it. The periosteal spindle and the periosteal lipping are seen. The tumor stops abruptly at the epiphyseal junction.

In the roentgenogram, the condition most frequently confusing the diagnosis of a malignant bone tumor is chronic low grade osteomyelitis. Because it is most frequently diagnosed erroneously in the presence of Ewing's sarcoma, the points differentiating it from malignant skeletal tumors will be discussed in detail later. The differentiation from skeletal tuberculosis will rarely cause difficulties in the diagnosis. The fact that osteogenic sarcoma is generally met with in young adults in apparently the best of health is in great contrast to tuberculosis which is usually observed in persons with a general condition below par. Sarcoma and tuberculosis also differ in location; e. g. osteogenic sarcoma very rarely if ever begins in the epiphysis of the bone while tuberculosis nearly always involves the joint end of the bone and primary diaphyseal tuberculosis, although known, is exceptionally rare. While in sarcoma the overlying skin is reddened early because of dilatation of superficial veins, in tuberculosis the skin is usually paler than normal.

Roentgenograms of osteogenic sarcoma in the same location in patients of about the same age reveal certain common characteristic features which may be best appreciated from a study of typical instances. I have attempted to present here as illustrations roentgenograms of characteristic types of osteogenic sarcoma

Fig. 52. Case 269. Osteogenic sarcoma of the myxomatous variety in a man 68 years old. Showing slight expansion of bone and a trabeculation of the medullary cavity.

Fig. 53. Case 535. Osteogenic sarcoma in a man 28 years old. The speckling in the roentgenogram is typical of osteogenic sarcoma of the upper femur, in the trochanteric region, due to excess of cartilage and calcification foci in it. Death 11 months after onset.

(Figs. 50, 51, 52, 53; Plate 13). Especial mention should be made of the variety of osteogenic sarcoma which is situated in the diaphysis of the femur. As it was pointed out above, about 8 per cent of all osteogenic sarcomata of the femur have such a location.

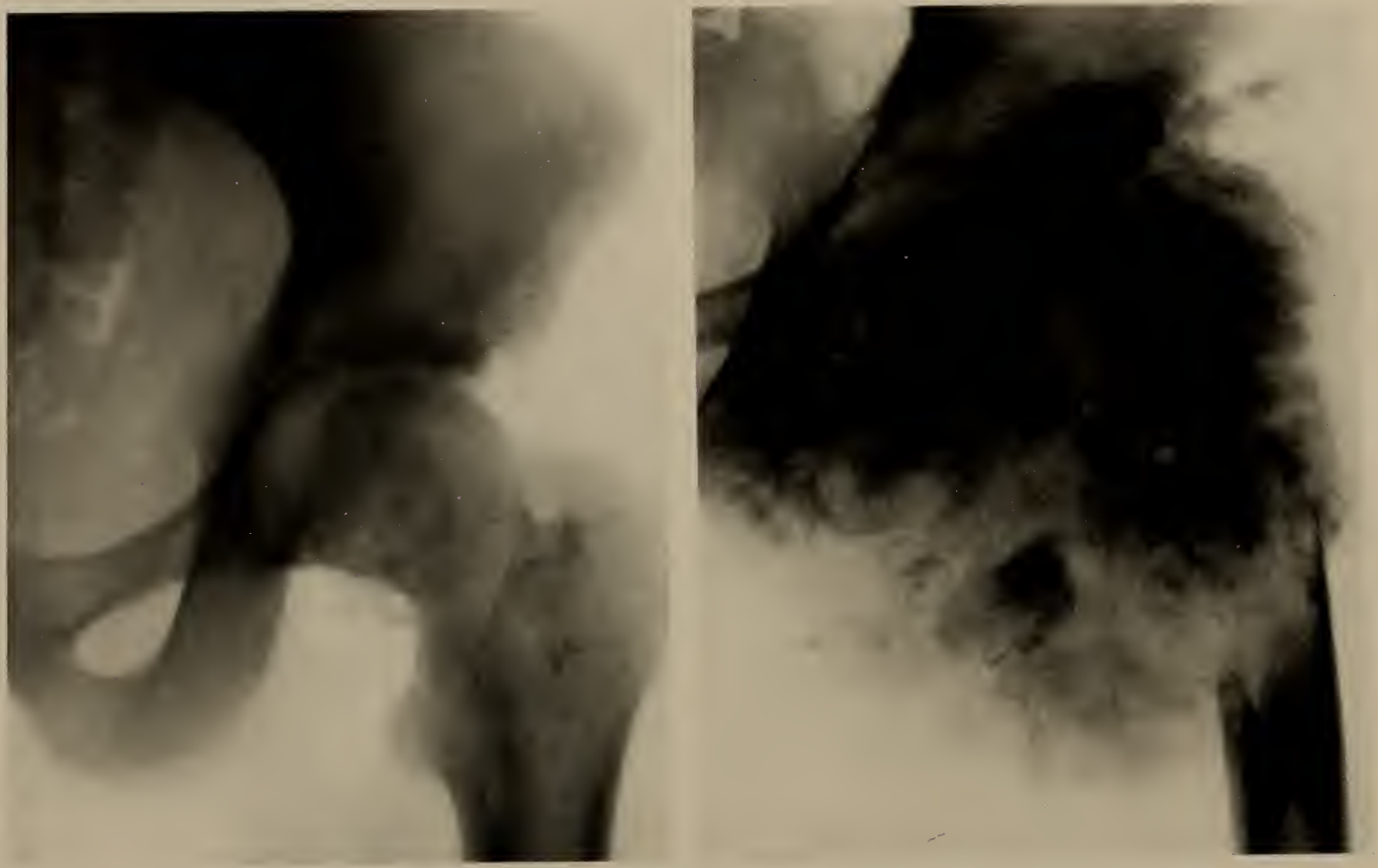


Plate 13. Personal observation; not registered. Osteogenic sarcoma in a boy 18 years old. Roentgenogram (left) taken 3 months after onset. An exploratory operation was performed at that time and the pathologist reported "osteomyelitis." Right, Roentgenogram taken 7 months after the onset.

It is with great care that a diagnosis of osteogenic sarcoma should be made when a tumor involving the midshaft rather than the end of the femur is met in a young individual, since such a location is characteristic of Ewing's sarcoma. A differentiation of such an osteogenic sarcoma from Ewing's sarcoma can hardly be made from the roentgenogram, save in the far advanced stage; a microscopic study is indispensable here. A careful follow up of the clinical course of this variety of osteogenic sarcoma seems to indicate that the tumor passes through two phases. The first phase is the osteoblastic; the bone is slightly expanded but distinctly denser than normal and no distinct tumefaction can be made out as yet. Then the disease enters the second phase; the bone becomes considerably widened, and at one point or another a rapid destruction of the bone commences (Plate 14). The widening of the shaft may be accompanied by the appearance of longitudinal striations (Fig. 54). With the progress of bone destruction a large extra-osteal tumor appears. The bone destruction is so rapid that a pathological fracture is not uncommon in these cases; the frequency of spontaneous fractures probably being augmented by the situation of the tumor in the middle of a long, weight-bearing bone. Occasionally myositis ossificans may be confused with this variety of osteogenic sarcoma. Unlike osteogenic sarcoma, myositis ossificans usually develops during the first three or four weeks after the onset with trauma with a subsequent period of quiescense. The consistency of the tumor in myositis ossificans is bony hard in contrast to the firm but resilient feel of osteogenic sarcoma (Plate 15).

While an attempt to diagnose a skeletal lesion suspected of malignancy from the clinical and roentgenologic angle does not involve any procedures which are apt to influence the natural course of the tumor in any way, an examination from the pathological angle is possible only after direct encroaching upon the tumor mass. This fact alone would seem to narrow the clinical importance of the pathological angle of examination as a preliminary step toward diagnosing the skeletal condition. The uncertainty of a clinical examination and the diagnostic limitations of roentgenology, however, foster the importance of the pathological angle of examination in these tumors. The frequently encountered regressive changes, spontaneous or after radiation, inflammatory changes, traumatic or of infectious nature, and various peculiarities of the histology of osteogenic sarcoma make it desirable to diagnose a malignant skeletal tumor from the gross appearance, without dependence upon the microscopical picture. As it is easy to see from the gross anatomy of osteogenic sarcoma, the prerequisite of such a diagnosis is wide experience in this relatively rare disease. A pathological diagnosis of malignant skeletal tumors is not always dependable and the personal equation of the pathologist counts greatly in the diagnosis; sometimes even a diagnosis based on examination of numerous slides of a bone tumor may not be correct. Such examinations are notoriously unreliable when the material to be examined

Plate 14. Case 639. Osteogenic sarcoma in a girl of 12. Notice location in the midshaft of the femur. Roentgenograms taken one month after onset showing bone denser than normal; and 4 months after onset showing tumefaction and extensive destruction of bone.

Fig. 54. Case 638. Osteogenic sarcoma in the midshaft of the femur in a girl 14 years old. Showing the combination of features of osteogenic sarcoma—radiating spicules; and of Ewing's sarcoma—the widening of the shaft and parallel striations. Death 3 years after onset.

Plate 15. Case 263. Myositis ossificans in a man 34 years old. The onset in July, 1919, with a tumor of the fibula (roentgenogram 1). In November, 1919, the involved part of the fibula was resected, but in February, 1921, a recurrence was noticed (roentgenogram 2). In February, 1923, an amputation was performed (roentgenogram 3). Notice the striations of the ossified muscle bundles. This case was interpreted by some pathologists as an osteogenic sarcoma.

consists of tumor tissue removed in biopsies. I have seen cases of osteogenic sarcoma in the Registry material in which repeated biopsies, even five in the same case (616), were made to secure tissue for diagnosis while the correct diagnosis became obvious after all these explorations only from the rapid growth of the tumor infected during the exploratory operations. It is easy to understand why, when the differential diagnosis of bone tumors is uncertain by any single method, there exists a tendency to "explore" the tumor and to shift the task of diagnosis to the pathologist. Although a biopsy of a bone tumor is frequently advocated by surgeons, it is significant that pathologists most experienced in bone tumors raise their voices against probatory incisions in cases of suspected malignant bone tumor. It would seem that the attempt to neutralize the bad effects of a probatory incision by intensive cauterization of the operative wound is unavailing, since the dangers of an exploratory incision are not merely the possibilities of dislodgement of metastases but also the surgical insult combined with the irritation of the escharotic used which may increase the rate of growth of the tumor. Cases have been seen in which an infection brought in during such an exploratory incision led to a stimulation of the growth of the tumor. It is true, of course, that frequently an exploration will relieve the patient of pain because of decrease of the tension beneath the periosteum, following the evacuation of sarcomatous tissue; but soon the tumor will begin to grow rapidly. If an exploratory operation is decided upon, it should be remembered that in tumors previously irradiated it may be difficult to secure a sufficiently vital and representative piece of tumor to warrant a histological diagnosis. In removal of tissue for diagnosis all the removed tissue should be saved, because the recurrent tufts mixed with granulation tissue and infection are dangerous for a histological examination and may lead to an erroneous diagnosis and sacrifice of the patient's limb in the presence of a benign tumor.

As a substitute for the harmful exploratory incisions in doubtful cases of bone tumor a therapeutic radiation test has been suggested. Recent experience has furnished sufficient evidence to justify the belief that radium or roentgen-ray radiation may frequently replace a biopsy. It may be safely stated that no skeletal lesion responds so rapidly to radiation as do certain types of malignant tumors. The most agonizing constant pain frequently disappears after one or two exposures. The rate of growth slows down remarkably so that a speckled and hazy roentgen-ray shadow of a diffusely and rapidly growing osteogenic sarcoma soon acquires a more or less well limited outline; the shadow becomes denser, more compact (Plate 16). The most rapid response to radiation is noticed in Ewing's sarcoma and cellular osteogenic sarcoma. The response is less frequent and prompt in acellular and highly ossifying tumors, although the subjective relief is frequent also in this variety. It is fully ascertained that a preliminary radiation test will frequently help one to arrive at a diagnosis without an exploratory incision. For

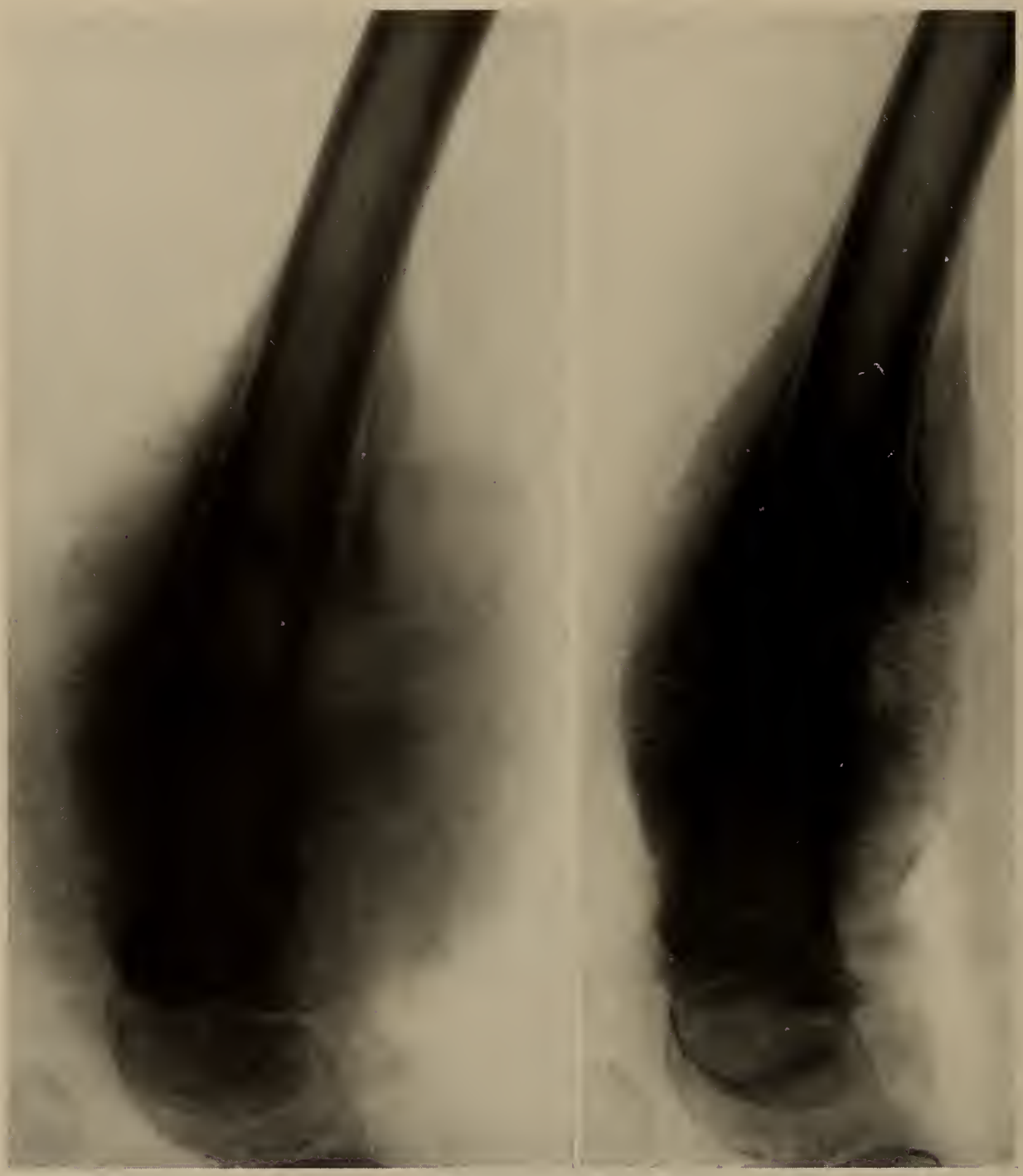


Plate 16. Personal observation; not registered. Osteogenic sarcoma in a boy 5 years old. Death 9 months after the onset. Showing the response of the tumor to radiation. Between the two roentgenograms an interval of 3 weeks has passed, during which time the patient was given 3 half hour exposures to 200,000 volts of roentgen rays.

better evaluation of the results of a radiation test it is important to have the roentgenogram of the lesion before and after radiation of equal density. To secure the latter it should be remembered that the density of a roentgenogram is the result of the intensity of exposure which is directly proportionate to the current, to the square of voltage, and to the time of exposure and indirectly proportionate

to the square of the distance of the tube from the film. The density also depends upon whether screens are used or plain films.

Therapy

In bone sarcoma as in other malignant tumors the question of the therapy is still awaiting its answer. It is a strange fact that with our knowledge of minute details of the histopathology of bone tumors the progress along the practical therapeutic road is almost in the same stage that it was in some fifty years ago. As a rule malignant bone tumors are fatal and we know of no therapeutic method to prevent death from this disease. Occasionally one sees in the literature the term "cure" in connection with bone sarcoma. The word "cure" is not to be taken in the real sense of the word, usually a five years' cure is understood; this term is valuable only in comparative studies. Patients with osteogenic sarcoma who were free of metastases for years after amputation have later died of pulmonary metastases. It is an exaggeration to say that a tumor from which the patient has recovered is not a malignant bone tumor; but in such a statement there probably is more truth than error. The relative individual character of the term "cure" is one of the reasons why all statistical data of cure from bone sarcoma through one or another method of treatment are nearly worthless. Too many subjective, unstandardized factors are in play in such statistics to render them of value; apart from what is meant by "cure" much depends upon the stage of the disease when treated, upon the method and character of treatment and upon other changeable factors. Mistaken diagnoses are not infrequent in such reports. Cases of osteitis fibrosa, skeletal syphilis, and other bony lesions, erroneously interpreted as sarcoma will obviously raise the frequency of "cure." Of the same value are also the reports of spontaneous cure of bone sarcoma. It is true that authoritative observers have described regression in growth and development after partial surgical removal but no authentic cases of malignant bone tumor can be found among the reports of spontaneous cures.

To the end of the past and the beginning of the present century belongs the origin of the immuno-therapeutic attempts to cure or relieve patients with malignant tumors including bone sarcoma. The sponsors of these therapeutic measures set out from a viewpoint that malignant tumors are of a parasitic infectious nature. These attempts are also based upon observations of spontaneous disappearance of malignant tumors after an erysipelatous infection of the patient. The toxin and sera therapy of malignant tumors form a most romantic chapter in the history of these diseases. Being enthusiasts, the authors were easily impressed by doubtful results readily explainable on other grounds. And truly, what could be more enchanting than to make the organism immune to the infectious, fatal tumor? One after another the various, ingenious methods of immunization and detoxication were raised merely to fall discredited.

From all the various attempts at specific therapy we have today left only Coley's mixed toxins. The theoretical idea underlying Coley's toxins is active immunization of the patient. After long experiments with numerous preparations of various streptococci with and without the combination with bacillus prodigiosus, Coley arrived at the following way of preparing his toxins. A ten day old agar culture of bacillus prodigiosus is sterilized by heat and added to a sterile three weeks old streptococcus broth culture in the approximate proportion of 100 cubic centimeters of streptococcus culture, 30 cubic centimeters of suspension of the prodigiosus culture, and 20 cubic centimeters of glycerin. This preparation is introduced subcutaneously or intratumorally. It is Coley's belief that if, after four weeks of intensive treatment with the toxins, no marked improvement is registered, then the expectations from this therapy are poor. When the tumor responds to the treatment, Coley recommends continuing this therapy for a year or longer. The usual reaction to a foreign protein, fever, chills, dyspnœa, vomiting, and general malaise, are not infrequently observed. From a study of the abundant literature of this subject and of the material of the Registry one cannot agree with the enthusiastic reports of Coley. Many advanced and inoperable cases which have responded well to Coley's treatment have proven to be giant cell tumors for which it is not very unusual to see spontaneous improvement after a pathological fracture. However, whatever one may think of Coley's toxins one is amazed at the sincere honesty and tireless ambition with which Coley has worked on the development of this method of treatment.

Of late we frequently hear of the importance of Coley's toxins in combination with roentgen or radium radiation. The fact that this new wave of enthusiasm for the toxin takes place in days when radiation is brought into extensive practice is apt to make very dubious the importance of the toxins in themselves. There is no proof, however, to deny the validity of the argument that toxins increase the effect of radiation. The question of the way Coley's toxins could influence the tumor is too obscure to be discussed here. A general reaction of the organism to a foreign protein is probably the best explanation. During the long history of the therapy of bone sarcoma there was a time when chemical therapeutic methods were in vogue. It is safe to say that nothing has been achieved in bone tumors from chemotherapy; formalin in 10 per cent solution is occasionally used in inoperable ulcerated tumors as a deodorant.

Until recently operative therapy of malignant bone tumors has been the method of choice. This despite the fact that with the highly developed surgical technique and skill it is still impossible by operative treatment to influence the metastases of the tumor latent in other organs. It is hardly necessary to argue here the evident fact that radical surgery alone is unable to solve the therapeutic question of bone sarcoma. At first glance it is strange that, although the experience of radical surgery has been disappointing, it has until recently dominated all

therapeutic considerations in bone sarcoma. In their attitude toward the question of operative treatment of bone sarcoma two extreme types may be observed among surgeons. To one belong those who, at a slightest suspicion of bone sarcoma, amputate the extremity. Their argument is plain; it is better to sacrifice a limb than the whole organism. Frequently in these cases the surgeon never knows the true nature of the lesion; all goes well, and the number of "cures" from surgical treatment is large. To the other extreme belong surgeons who will doubt the diagnosis of malignancy in the absence of any of the characteristic symptoms of the disease, frequently despite a histological diagnosis. To these surgeons malignant bone tumor also spells amputation, a most radical operation to avoid which the diagnosis is doubted until, as a court of last resort, amputation is performed. Procrastination and delay here make the amputation entirely futile from the start.

From an analogy between bone sarcoma and carcinomatous tumors a question suggests itself: could not an early diagnosis combined with radical surgical treatment solve the problem of therapy in bone sarcoma as it occasionally does in some types of early diagnosed and well localized carcinomatous lesions? There is abundant evidence on hand to the effect that nothing is known that would help to establish a diagnosis of bone sarcoma in an incipient stage. Instances of osteogenic sarcoma are occasionally seen in which in spite of the fact that an amputation is made a few weeks after the subjective onset of the disease, death follows from pulmonary metastases. This would seem to indicate that a metastatic dislodgment of a malignant bone tumor is incomparably more rapid than in malignant tumors in soft organs or, what is more probable, that the subjective onset does not correspond to the true onset of the disease, which passes on unnoticed and gives rise to metastases before it attracts the attention of the patient.

In the consideration of the question of the indications for radical surgical treatment in a case of osteogenic sarcoma there are certain conditions which play a decisive rôle. The main condition is certainty of the diagnosis. In the large majority of cases the experienced diagnostician will arrive at a definite diagnosis from a careful analysis of the clinical and radiological data and of the result of the therapeutic radiation test. There will be, however, in exceptional cases times when the experienced observer will be unable to arrive at a definite diagnosis; in these cases an exploratory incision will be unavoidable. In such cases the surgeon must be prepared to act according to the diagnosis, and before operation he must have the consent of the patient to amputation. To explore simply for diagnosis and then to institute conservative treatment in case of malignancy is one of the most radical mistakes made. For the clinician well acquainted with the gross pathology of bone tumors, an exploration with an application of two constrictors is of real value; the distal constrictor is to prevent dislodgment of

Plate 17. Courtesy of Dr. Baker, Newark; not registered. Osteogenic sarcoma in a boy 16 years old. The roentgenogram was taken 2 weeks after the clinical onset of the disease. Very little is to be seen in the roentgenogram except for a slight jagging of the internal aspect of the femur (arrow). A roentgenogram of the chest made on the same day revealed far advanced pulmonary metastases.

metastases from the area of exploration while the proximal constrictor is for an immediate amputation should the tumor be found malignant.

The second condition in the consideration of indications for radical surgical treatment is the old rule in surgery of malignant tumors, "all or nothing." Do not operate if you think that complete removal and eradication of the primary tumor is impossible. This rule alone excludes surgery in osteogenic sarcoma of the spine, skull, and pelvis.

Another condition upon which an indication of surgical treatment is based is absence of clinical evidence of metastatic generalization of the tumor. A radiological examination of the lungs is required before instituting surgical treatment in osteogenic sarcoma (Plate 17); small metastatic foci which cannot as yet be perceived by percussion and auscultation will frequently be demonstrated in the radiogram as light, cloudy spotting in the normally dark lung shadow in the film. A preliminary radiological examination of the whole skeleton will occasionally save the surgeon from disappointment when multiple tumors or bone metastases are present. As exceptions to all these requirements for indication of radical surgical treatment are patients suffering unbearable pain which cannot be ameliorated by radiation. In such patients surgical treatment should be considered even in the presence of features which in an ordinary case will contraindicate such treatment.

After the indication for operative treatment has been established a question will arise of choosing between a conservative surgical procedure and a radical one. This question is almost as old as surgical therapy of malignant bone tumors itself. It was Mikulicz who first emphasized the advantages of tumor excision and bone resection over amputation and disarticulation. There is little if any difference between these two methods of surgical treatment, radical and conservative, as far as metastases are concerned, and if the resection or excision of the tumor is well done there is no reason why metastases should be more frequent than after an amputation. However, the main motive pointed out by Mikulicz, that a patient will sooner meet the necessity of a resection than a crippling amputation has lost ground at the present time with the high development of prosthetic surgery; it is indeed well known how very frequently an artificial limb is of incomparably more use and comfort to the patient than a leg with a stiff joint or with a constantly aching bone. Bloodgood has frequently mentioned that it is not unusual for his patients to become more efficient after an amputation; an artificial limb is frequently well borne by young patients even in dancing. It is true that in many cases the tumor can be removed just as completely by resection as by amputation; however, the hazards of the operation in connection with the dangers of overlooking involved tissue are great enough to strip the method of resection of all advantages over a more radical procedure, and unless the tumor involves a region for which no satisfactory artificial limb can be fitted, amputation is to be

preferred to any conservative surgical procedure. To resect the tumor and graft bone in a patient with an osteogenic sarcoma is an unwise procedure, not in accord with the palliative character of the operative measure.

If the choice between resection and amputation can be argued by a surgeon experienced in bone pathology, it is entirely out of place when the patient is in the hands of the surgeon operating only occasionally for bone tumor, for whom the method of choice is amputation or disarticulation if operative treatment has been decided upon. But even before the experienced observer decides to excise or amputate, it is advisable as a preliminary step in the operation to explore the main blood vessels, since if these are surrounded by tumor, amputation is the only choice. It is significant that the surgeons most experienced in bone tumors at the present almost wholly prefer amputation to resection or excision.

Excision usually comes up in borderline cases of bone tumors like skeletal chondroma. With this tumor any partial, conservative operative procedure is dangerous; indeed, no operation which leaves a trace of these quasi pedunculated tumors should be advised. It should be remembered that the apparent gross integrity of the cortex of the bone to which the tumor is attached is not dependable. In excising these tumors it is best to chisel away liberally the cortex upon which the base of the tumor rests.

Another conservative surgical procedure which dates back at least 50 years is ligation of the main artery supplying the region of the tumor involvement (Plate 18). In the literature one finds indications that sometimes such a ligation in a telangiectatic sarcoma leads to healing of the tumor for years. Recent attempts to influence a very vascular sarcoma by means of ligation of the afferent artery were unsuccessful, thus throwing a shadow of doubt upon the true sarcomatous nature of the tumors reported in the old literature.

Whatever the operative procedure decided upon, whether amputation or excision, it should be kept in mind that in muscles the spreading of sarcomatous tumors may easily be overlooked, and since the tumor, after perforation through the investing capsule, rapidly spreads along the intermuscular septa an extensive dissection of the muscles is most important. If operation is going to help temporarily, amputation of the involved bone may be sufficient, and a disarticulation of the proximal joint is unnecessary. Death takes place not from a recurrence because of a low seat of amputation but because of lung metastases which cannot be prevented by disarticulation. I have seen cases in which midthigh amputation in osteogenic sarcoma of the lower end of the femur was not followed by recurrence locally but by pulmonary metastases. Occasionally one is, however, misled by the roentgenogram if one depends upon it entirely in choosing the seat of amputation; since the medullary cavity may be stuffed with tumor while in the roentgenogram this portion of the bone will appear normal (Fig. 55). Here again one sees the necessity for the surgeon undertaking surgical treatment of

Plate 18. Case 508. Same case as that in Figure 7. Osteogenic sarcoma in a girl 5 years old. A very vascular "telangiectatic" tumor in which ligation of the afferent artery as a therapeutic measure suggests itself.

bone tumors to be well acquainted with the gross anatomy of these lesions. The ease with which an involvement of bone-marrow at the point of amputation may be overlooked explains the preference for disarticulation over amputation among surgeons years ago. Experience has shown, however, that the results

Fig. 55. Case 382. Osteogenic sarcoma in a boy 18 years old. Roentgenogram was taken 4 months after the onset; it shows an intact outline of the cortex of the bone. Disarticulation was performed at the same time and an extensive sarcomatous involvement of the medullary cavity was found; the involvement extended down past the middle of the shaft. Death 7 months after onset.

after disarticulation of the hip do not differ from amputation distal to the hip joint as far as secondary growths and recurrences are concerned. On the other hand, in exceptional instances even disarticulation is not sufficient for avoiding a local recurrence; for example, in sarcomata of the upper half of the humerus where a complete shoulder girdle extirpation (amputatio interscapulo-thoracalis) promises far better results as far as local eradication of the tumor is concerned.

The vast accumulation in recent time of technical knowledge and the advance in the application of radiation, roentgen ray and radium, in the therapy of malignant tumors in general required a re-evaluation of all accepted principles and traditions as far as the therapy of bone sarcoma is concerned. Even now clinicians are inclined to think that if a bone sarcoma is operable there is an indication for surgical treatment without losing time in radiation, while for radiation treatment only the inoperable cases are to be left. That this view is obsolete and not in accord with the disappointing results in radical surgical treatment is obvious. It is true that no astounding success has as yet been achieved by radiation therapy of malignant bone tumors and that most results here are unsatisfactory; however, the evidence on hand is encouraging, and radiation is as legitimate a therapeutic procedure in bone sarcoma as radical surgery.

Radiation therapy is still in the experimental stage, and institutions lacking the best available modern apparatus and specially qualified personnel should refrain from making wide use of it. Unfortunately we are witnessing at the present time a wide popularity of radiation therapy among persons lacking the necessary experience and skill. It is obvious that since, to the average inexperienced radiologist, the possession of an X-ray machine and radium means he is qualified to administer radiation, considerable abuse and misuse of radiation in bone tumors may be expected. Only with a vast clinical material and under prolonged, careful observation will this promising method of therapy become definite. Abuse of radiation by incompetent persons will not only greatly contribute to the confusion already overwhelming this new field of medicine, but it is also connected with great dangers for the patient. That errors in technical application of radiation may do harm is a fact fully ascertained. Whatever the true biological cause of the influence of radiation upon living tissue may be, it is attested that this action will be stimulation or inhibition depending upon the dosage together with technical factors from a detailed discussion of which I must refrain here. That inefficient radiation may stimulate the tumor growth has been emphasized repeatedly. On the other hand, over-radiation is dangerous for the normal structures of the organism. Excess of radiation may lead to ankylosis of an exposed joint. The skin becomes bronzed and leathery, and ulceration of the skin may ensue. The bones become sclerotic, ivory-like, and spontaneous fractures of such bones evince a definite delay in union. The marrow cavity becomes obliterated from over-radiation (Plate 19). Obliteration of capillaries

Plate 19. Case 365. Osteogenic sarcoma in a woman 25 years old. Excessive roentgen-ray radiation rendered the bone sclerotic and brittle with a pathological fracture as a result. The medullary cavity of the bone is narrowed; extensive degenerative changes in the tumor are seen, probably from radiation.

of the periosteum and endosteum causes a scarcity of callus formation in fractures. All these changes following over-radiation may be accompanied by severe pain. It is hardly necessary to argue here that in such complex biological processes as the influence of radiation upon the tumor and the organism no hard and fast rules about the dosage can exist. The reaction to radiation of similar tumors in two individuals may be very different. Only the experienced radiologist is qualified to decide the question of the dosage in each individual case. Among the various methods of application of radium the intra-tumoral application of radium recently has gained a recognized place. This procedure is hardly justified; it carries the dangers of an exploratory incision without its advantages.

The influence of radiation upon the general condition of the patient was mentioned elsewhere, as well as the influence upon the tumor itself. Radiation

leads to a conversion of a cellular tumor into a quiescent bony mass, which in large vascular tumors may contain hæmorrhagic cysts and necrotic material. In tumors with an abundant intercellular substance the response to radiation according to the present-day technique is not as effective, however, instances of calcification and ossification of the tumor combined with a retardation of growth of the tumor from radiation have been reported and are very encouraging. It is true that the cessation of growth of the tumor from radiation is merely temporary and the patient dies from local recurrence and pulmonary metastases. Thus radiation is as disappointing as radical surgery, but the difference in the sacrifice the patient has to make for radiation as compared with radical surgical treatment is enough to justify the former procedure especially since it is still in the experimental stage, when the last word has not as yet been spoken. When we learn more about the biology of radiation and acquire the same skill in administering radial therapy as we possess in using the scalpel we may hope for far better results from radiation.

The influence of radiation upon metastases is worthy of notice. I have seen cases in which the radiological evidence of pulmonary metastases has entirely disappeared from radiation and not returned for over two years; more frequently one sees pulmonary metastases kept checked by repeated radiation of the chest (Plate 20). A direct prophylactic radiation of the lungs is always indicated without regard to the method of treatment of the primary tumor whether by surgery or radiation.

Along with the rapid response to radiation of cellular and vascular osteogenic sarcomata there are some varieties which are little affected by radiation or not affected at all. To these belong tumors with a preponderance of myxomatous tissue, the skeletal chondromata and the so-called sclerosing osteogenic sarcomata. In other words, only if the tumor did not proceed in its differentiation farther than the myxomatous stage it is influenced by radiation. Moderate but persistent radiation may occasionally cause further calcification of a skeletal chondroma; radiation here leads to shrinkage of the blood supply while repeated partial surgical operations tend to increase the blood supply of the tumor. However, experience shows that skeletal chondroma of the recurring type is not suitable for radiation and should be attacked radically by surgery.

It is easy to see from the above that no generally accepted routine solution of the problem of treatment of osteogenic sarcoma is possible at the present time; and while some authoritative observers advocate amputation followed by prophylactic radiation of the lungs, others treat the patient with radiation and keep him comfortable; they think that the general comfort and well being of the patient while he is living is greater under radiation than if amputation is done. From the observations made in the foremost institutions of the country during recent years one is strongly impressed by the need of intelligent co-operation

Plate 20. Case 523. Osteogenic sarcoma. Illustrating a disappearance of pulmonary metastases after radiation. The primary tumor was in the left iliac bone in a woman 35 years old; the onset in January, 1920. In January, 1921, an exploratory incision was made. The diagnosis of osteogenic sarcoma was proven by the extensive pulmonary metastases which were demonstrated clinically and radiologically in December, 1922. Heavy roentgen radiation was followed by a marked constitutional reaction lasting 3 weeks, after which time the lungs began to clear up. Roentgenograms taken December 26, 1922, (left) and January 17, 1923.

between the clinician, radiologist and pathologist in combating this grave disease. Without desiring to seem dogmatic I find the following way probably best in caring for a patient with a typical non-sclerosing osteogenic sarcoma. Immobilization of the extremity and recumbency are followed after a few months of efficient radiation by amputation. Moderate prophylactic radiation of the chest is to be continued throughout the whole course of the disease. It is important to avoid over-radiation. Borderline cases should be treated as typical osteogenic sarcoma. Occasionally in far advanced cases immediate amputation may give the patient a few months respite from invalidism and agonizing pain.

Prognosis

A prognosis as to life expectancy in bone sarcoma is only of relative value since the natural history of the tumors which come under observation is usually changed by surgical and other therapeutic procedures. Prognosis based solely upon results of surgical treatment is of questionable importance because many individual factors, like the type of tumor, the stage of development, individual judgment in selecting cases for surgical treatment, all have a close bearing on the final result. In general no blanket rules can be made as to the prognosis of bone sarcoma. The attempts of pathologists to form a prognosis of a tumor from its pathological and morphological features alone has nowhere failed more than in bone tumors. Now and again one sees two cases with a very similar histology, one quickly ending fatally and the other going on for a much longer period of time. The histological structure, to be sure, is important since it indicates the potential malignancy of the tumor but this is merely one link in the whole chain of circumstances which render a tumor malignant. In this chain much depends upon pure clinical evidence. Of prime importance also are the gross pathological features of the tumor; they are easier to interpret, less fallacious and therefore more reliable than the histological structure, especially in the hands of those who have had a limited experience in the histopathology of bone tumors. When in malignant bone tumors the clinical course is not in accord with the histological characteristics, this discrepancy is frequently a result of deficient study of the clinical data and the gross appearance. To be of value prognosis should be determined in the light of all data available; the clinical, radiological, and pathological. The most important points of the clinical, radiological, and pathological examination for prognosis have been emphasized in the corresponding chapters; only a few points requiring greater stress will be mentioned here.

The age of the patient with an osteogenic sarcoma is important in determining the prognosis, since adolescents are less able to withstand the disease than persons above 30 years of age. In children the prognosis is still worse because of the rapidity of growth and the early appearance of metastases. The grave prognosis in the young is well in accord with the repair-and-loss-of-growth-

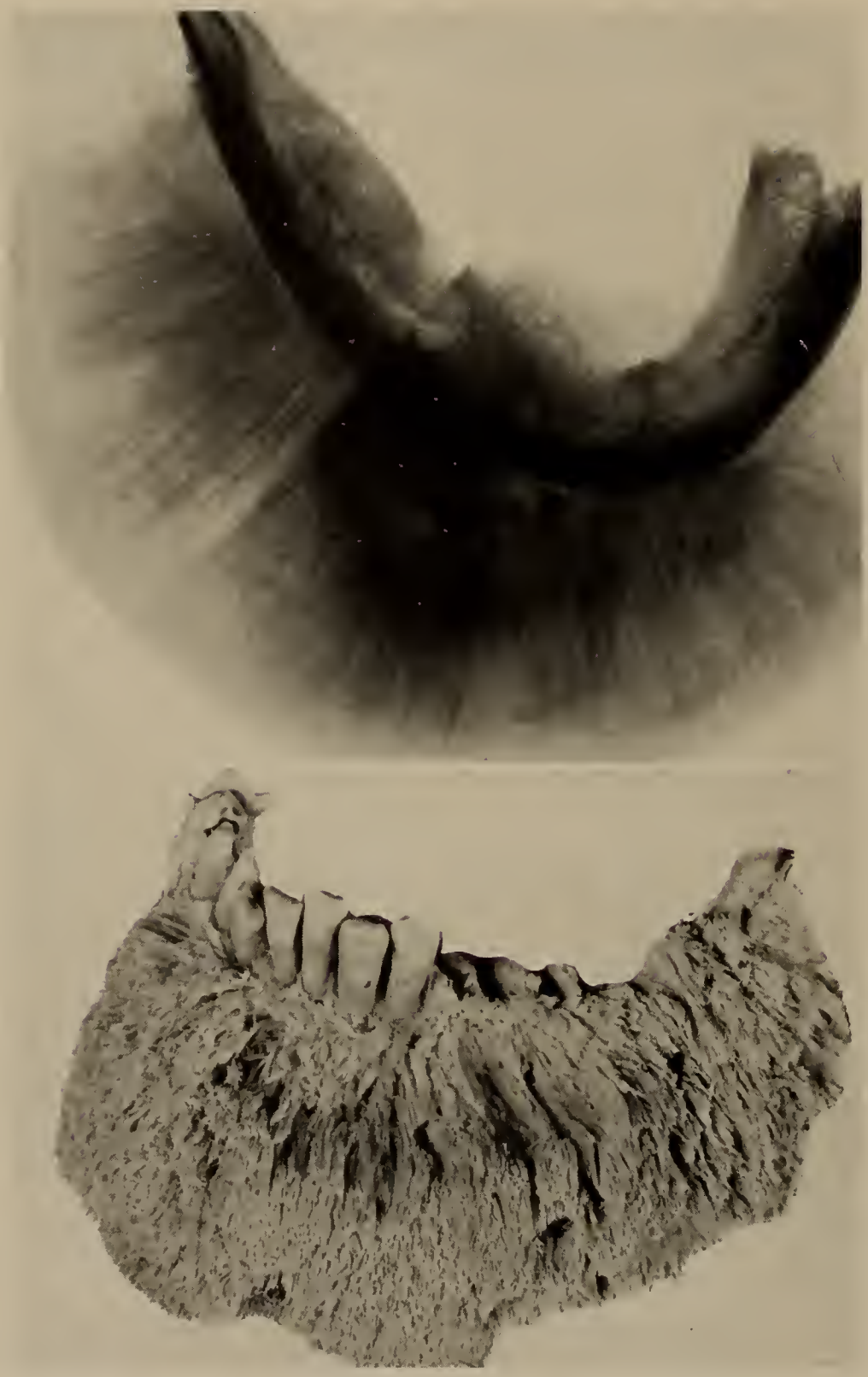


Plate 21. Courtesy of Warren Museum, Boston. Osteogenic sarcoma of the mandible. Classical roentgen-ray appearance. The photograph of the macerated and dried specimen shows the ray-like lamellæ of bone forming the skeleton of the tumor.

Plate 22. Case 404. Osteogenic sarcoma in a man 25 years old. Typical specimen and roentgenogram.

restraint theory of the origin of osteogenic sarcoma; if the tumor is a result of repair in the presence of a loss of growth restraint, then in the young a similar repair is far more dangerous than in the adult. The next features of prognostic importance are rapidity of growth and duration of the disease. A tumor of long standing is usually slow growing and is apt to be benign; however, the rate of growth may be entirely altered by trauma, accidental or surgical, after incomplete removal or exploratory incision. Extremely malignant osteogenic sarcomata usually are rapidly growing from the start. All other conditions being

equal, prognosis will change with the location of the tumor. The statistics frequently produced in the literature demonstrating the malignancy of a tumor in relation to its location are too dogmatic to be of real prognostic value. It is, however, sufficiently ascertained that in osteogenic sarcoma situated in or near the trunk the prognosis is very grave. Of extremities the gravest prognosis have sarcomata situated in the femoral neck. This is partly due to the thickness of the soft tissues covering the bone and consequently the late appearance of objective signs. Osteogenic sarcoma here if operated on has a worse prognosis than when situated in the upper portion of the humerus; the technical possibility of extensive removal of soft tissues infiltrated by extensions from the primary tumor is much greater in tumors of the upper end of the humerus than in the corresponding portion of the femur. The advisability of substituting the simple disarticulation of the humerus, in involvement of its upper end, by a complete removal of the shoulder girdle was mentioned elsewhere. The same operative procedure does not appreciably influence the prognosis in osteogenic sarcoma of the scapula. The indication in the recent continental literature of five years' cure in about 30 per cent of cases of "bone sarcoma" of the scapula are misleading since the authors seemingly did not discriminate between the types of tumors included in their reports. As a matter of fact, no osteogenic sarcoma of the scapula in the Registry has lived over three years after a radical removal. Of equally serious prognosis are osteogenic sarcomata of the clavicle, despite the fact that the clavicle can be easily removed without greatly impairing the function of the extremity. Sarcoma of the bones of the feet and hands are not so aggressive; they are early accessible for surgery and especially for radiation. The better prognosis here is perhaps due to the fact that a true osteogenic sarcoma of these bones is rare, most tumors here being extraperiosteal or of the surrounding soft tissue, with a fair prognosis. The osteocartilaginous tumors of the jaw are supposedly less malignant than similar tumors of long bones. This is probably due to the slower growth of the tumor in the jaw. Here recurrences after surgical removal are more frequent than distant metastases. The difficulty of removing the tumor which in the jaw is rarely well limited in a way that would insure against a local recurrence is probably a satisfactory explanation of it; recurrences are observed before distant metastases are recognized (Plates 21 and 22).

Not infrequently one is forced to determine the prognosis after the patient, operated on elsewhere, presents a recurrence or metastases. In itself a recurrence is no absolute proof that the original tumor was malignant. Incomplete removal of a benign tumor may result in a recurrence. That malignant tumors recur more frequently is largely due to the fact that a complete removal of a malignant tumor is much more difficult on account of its infiltrative growth. The presence of a recurrence in osteogenic sarcoma is not to be taken as a sign

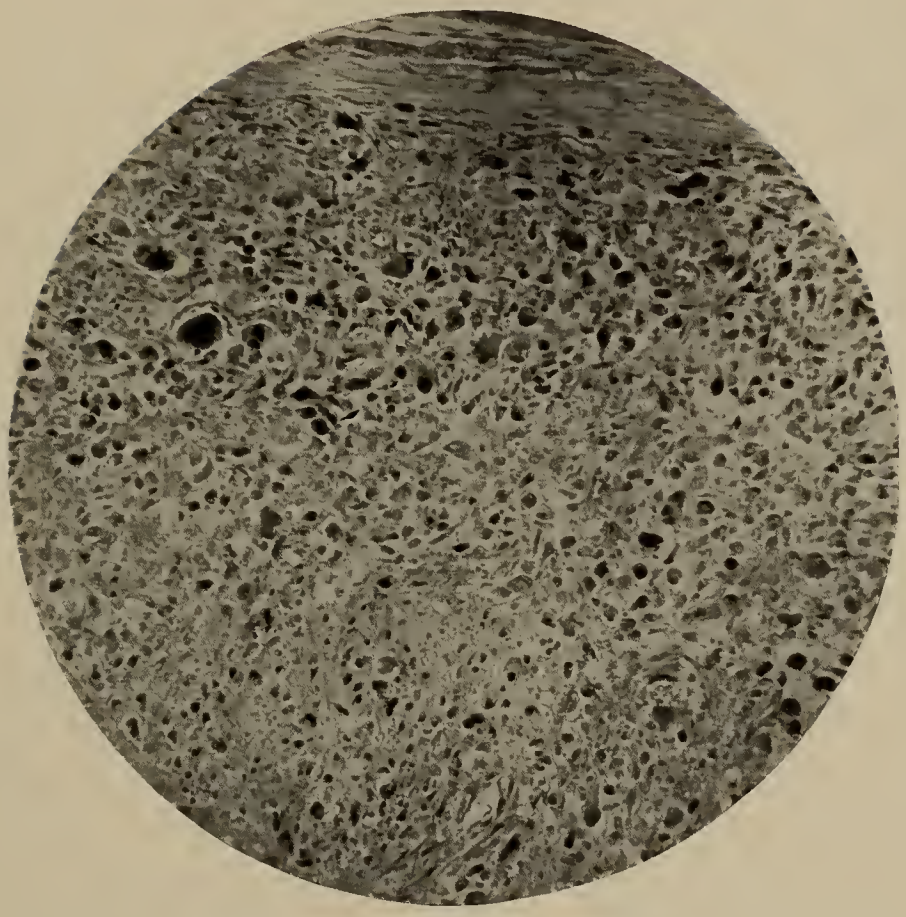


Fig. 56. Case 271. Same case as in Figure 57. Osteogenic sarcoma. Illustrating the variety of structure in different portions of the same tumor. The shown section was taken from an area close to the periosteum.

of impending death; a fatal end is imminent but the patient may go on for months. The utmost care is necessary in determining the prognosis from a recurrence if it is ulcerated; the tufts of tumor tissue as seen after exploratory incisions are usually infected and dangerous for the basing of a diagnosis or prognosis. Usually recurrences appear in osteogenic sarcoma during the first two years; however, exceptional cases are known of recurrence after a much longer interval of time. In such instances there will always be some doubt of the true nature of the growth. In the presence of metastases the prognosis must be given with reluctance; as was mentioned elsewhere, pulmonary metastases can be kept in check for a time by radiation, and even a complete disappearance of the evidence of pulmonary metastases after radiation is known to occur.

The great importance of the date of the radiological examination for the diagnosis of osteogenic sarcoma was outlined above. Attempts were made to draw conclusions from certain radiological features of osteogenic sarcoma as to the prognosis—for example, the favorable prognosis in the so-called sclerosing sarcoma, the better prognosis in osteoblastic osteogenic sarcoma as compared

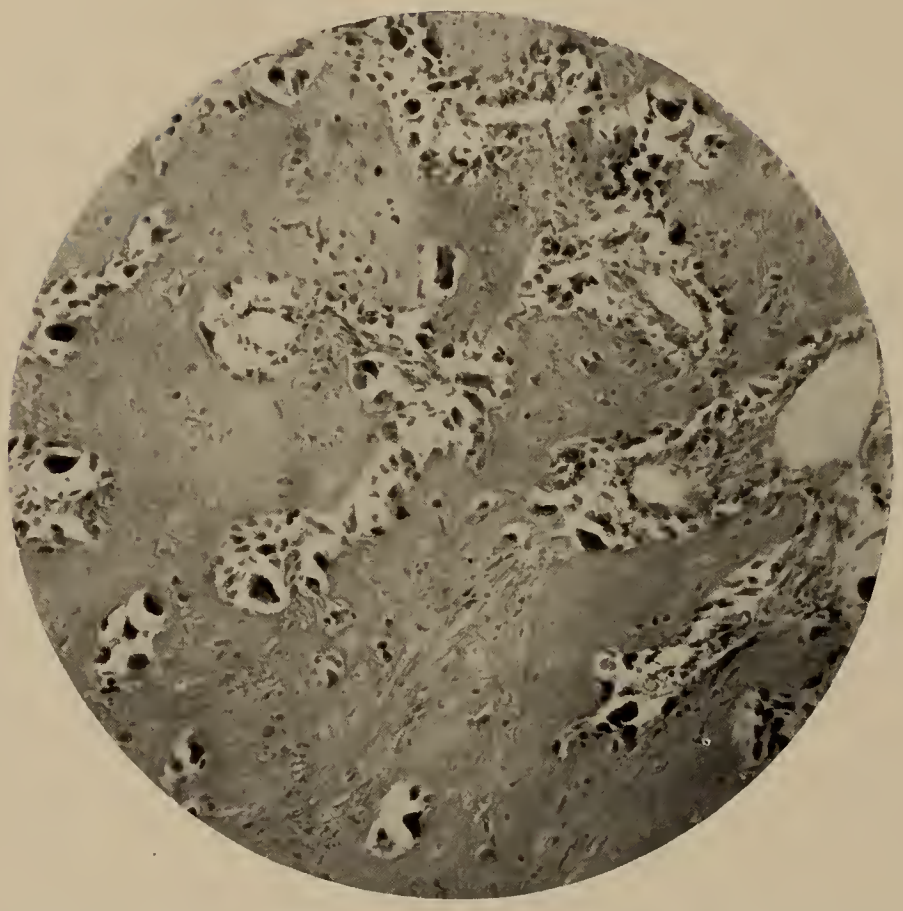


Fig. 57. Case 271. Compare with Figure 56. This section was taken from the central portion of the tumor; showing a relatively acellular hyalinized cartilaginous matrix.

with osteolytic osteogenic sarcoma when little or no ossification is seen in the roentgenogram. The utmost care is to be exercised in the prognostic evaluation of the radiological evidence. It is known how frequently a typical sclerosing osteogenic sarcoma in the roentgenogram will show numerous cellular areas; it is also generally admitted that radiation may convert a feebly osteoblastic osteogenic sarcoma into a definite osteoblastic growth in the course of several weeks. That ossification is not a dependable sign of better prognosis is evident from the fact that in the young ossification is more frequent despite the poorer prognosis than in the adult. The roentgenogram, however, is one of the most important single findings which will at once allow conclusions as to the diagnosis, stage of development, size and differentiation of the tumor.

A prognosis based upon clinical and radiological data may be greatly strengthened by findings of gross pathology and histopathology. The size of the tumor is the first factor of prognostic importance that impresses one; it is obvious that with a tumor reaching a large size without the presence of evident metastases the prognosis is better. Highly malignant bone tumors kill before they reach a large size. Encapsulation of the tumor is an important point in prognosis.

Prolonged encapsulation is a favorable sign, as very malignant osteogenic sarcomata early perforate the periosteum. Extreme vascularity of the tumor is a dangerous sign; the very vascular, so-called telangiectatic osteogenic sarcomata deserve a grave prognosis. The histological structure is an important factor in the prognosis when taken with other data, clinical, radiological, and anatomical.

The realization of the fact that the histological structure is of significance in prognosis has been greatly discredited by the assumption that all tumors may be divided in well defined groups each with an exactly defined grade of potential malignancy. The prognostic interpretation of histological findings is to be based upon the indications of the rapidity of growth of the tumor evinced by the histological structure of the tumor. The differentiation of the tumor cells is important in prognosis because an adult type of cells is usually found in the slowly growing tumors. The activity of cell division and hyperchromatism is significant as an indication of the rapidity of growth. The vascular channels and spaces lined by tumor cells characteristic of malignant sarcomata are another sign of rapidity of growth and hence of malignancy. This intimacy of tumor cells to blood vessels is important because of the readiness with which metastases may be dislodged. Necrosis if not due to radiation, is a sign of rapid growth and speaks for malignancy. Uniformity of cell structure, size and shape is a favorable sign, although pleomorphism is not an absolute indication of a grave prognosis. Tumors with a small spindle cell type have a grave prognosis.

A fact which seems to indicate a more favorable prognosis is the lymphocytic infiltration of osteogenic sarcoma. The lymphocytic infiltration was observed in 9 out of the 13 osteogenic sarcomata with five years' cure generally accepted by the Registry. The presence of the lymphocytes is not understood and involves doubt as to the diagnosis of osteogenic sarcoma in these cases; especially since the lymphocytic infiltration is rarely seen in osteogenic sarcomata which end fatally and are not incised previous to the amputation.

With the great prognostic importance of the histological structure of osteogenic sarcoma one should remember that one is not to depend entirely on the histology in deciding the prognosis if no examination of tissue from various portions of the tumor has been made; very frequently in osteogenic sarcoma one portion of the tumor differs greatly from the rest of it (Figs. 56, 57).

The few cases of osteogenic sarcoma with a five year cure in the Registry material are not sufficiently indicative to allow any general conclusions, for there is every reason to believe that the individual surgeon is more prone to register a success than a failure. On the other hand there are a large number of cases in the Registry in which the patients are still alive and have not yet reached the five year limit. Making allowances for all these arguments the very limited number of cases with a five year cure can not but greatly impress upon us the exceedingly grave prognosis of osteogenic sarcoma.

EWING'S SARCOMA

PATHOLOGY—*Gross Anatomy*

THE gross anatomy of Ewing's sarcoma is characteristic and varies from that of osteogenic sarcoma. In contrast with the latter this tumor favors the smaller bones of the extremities and the skull. When in a long pipe bone, it usually affects the shaft of the bone and not the ends. Another striking feature in which this tumor differs from osteogenic sarcoma is in the wide involvement of the shaft. The pathology of Ewing's sarcoma is less complex and easier to understand than the pathology of osteogenic sarcoma. The gross anatomic appearance in Ewing's sarcoma is mainly a result of the aggressiveness of the tumor cells, of the protective defensive measures of the affected bone, and of the regressive changes in the tumor mass. The tumor seems to begin simultaneously in numerous areas of the involved portion of the bone, in the bone-marrow filling the medullary cavity as well as the larger haversian canals. These diffusely disseminated multiple foci of tumor rapidly enlarge, become confluent, and show a great tendency to expand in all directions. The medullary cavity is frequently extensively involved at a very early stage when the cortex appears grossly intact. Fighting for space in the haversian system, the tumor diffusely dissolves the cancellous bone. The tumor cells readily spread between the bone lamellæ, which they separate and push apart. As a result of this separation of the bone lamellæ the tension and pressure lamellæ of the involved portion of bone stand out clearly in the roentgenogram (Fig. 58). This separation of the bone lamellæ causes the bone to appear in the roentgenogram thicker than normal, as if œdematous. At a very early stage of growth of the tumor the resemblance of the bone involvement to osteomyelitis is surprising (Plate 23). The resistance of the cortical bone is soon overcome by the tumor cells which rarefy and diffusely dissolve the bone from within the numerous haversian canals. With the approach of the tumor cells to the outside of the bone the periosteum proceeds to its protective reaction. A shell of new formed bone appears as a reinforcement to the bone reduced in strength. Soon the tumor cells penetrate this advancing layer of bone and spread along its external surface. A new layer of bone is laid down by the periosteum. Shell after shell of newly produced bone is permeated by the tumor until finally the periosteum is overcome in its race with the tumor and the tumor perforates the periosteal investing capsule and begins to infiltrate

Fig. 58. Case 385. Same case as that in Plates 26 and 27. Ewing's sarcoma in a boy 8 years old. This roentgenogram was taken 1 year after the onset. Showing the separation of the tension and pressure lamellæ of the involved os calcis.

the soft tissues about the affected bone. The spreading of the tumor through the haversian system with the gradual destruction of the affected bone and the newly formed bony onion-like layers parallel with the shaft, result in the characteristic diffuse displacement of the bone by the tumor mass. To this are added the occasional foci of calcification seen in the tumor. Along with forcing its way through the bone the tumor shows a great tendency to spread up and down the shaft. The very rapid growth of the tumor in some instances prevents the periosteum from forming a true bone shell and the periosteum is pushed away by tumor tissue; when the latter has undergone necrosis it leaves a cavity running beneath the periosteum up and down the shaft. Necrotic liquefied tumor tissue occasionally resembling gross pus may fill the cavity.

The consistency of the tumor depends somewhat upon the stage of growth and the regressive changes which have taken place in it. In the very early stage of growth when the tumor is grossly limited to a relatively small area of bone the tumor presents a soft mushy white grayish substance pressed into the empty

Plate 23. Case 161. Ewing's sarcoma in a boy 13 years old. The roentgenogram and specimen show the condition 3 weeks after the onset. Notice the onion-like layers in the roentgenogram and the diffuse involvement of the bone-marrow, with a permeation of the cortex by the tumor.

spaces resulting from focal bone absorption. It resembles the appearance which one encounters in osteomyelitis with granulation tissue filling up the chambers between the necrotic bone trabecula. In later stages of growth when only traces of remaining bone are seen in the tumor tissue, the tumor represents a soft medullary crumbly growth which has extensively destroyed the shaft of the bone and infiltrated the soft parts about it. This diffuse involvement of the

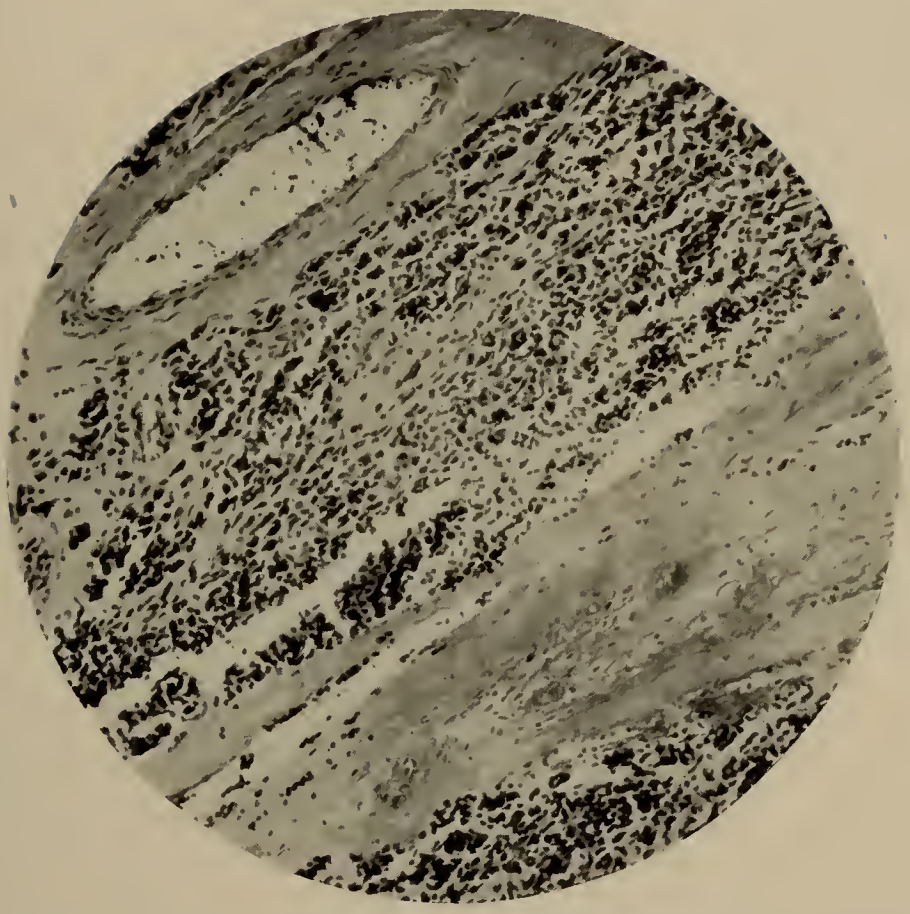


Fig. 59. Case 173. Same tumor as that in Plate 31. Ewing's sarcoma. Coherent pavement sheets of cells without definite structure formation.

surrounding fascia and muscles, however, may be outlined by a distinct thin pseudocapsule, which disappears at the advanced stage of the tumor. The only supporting stroma of this very cellular brain-like tumor mass are strands of coarse connective tissue ramifying in the tumor and subdividing it into lobules.

The consistency of the tumor greatly depends upon its vascularity. While the blood supply here does not reach such extremes as in osteogenic sarcoma, still the degree of vascularity differs enough in various cases to influence the consistency of the tumor. As in other cellular tumors, regressive changes are not uncommon in Ewing's sarcoma. Necrosis in tumor areas with liquefaction may greatly resemble gross pus. In some instances such regressive changes may result in cystic formations with yellow or red jelly-like contents.

Structure

Unlike that of osteogenic sarcoma the histology of Ewing's sarcoma is simple. The type cell is small polyhedral with round oval or slightly elongated nucleus with scant clear stainless cytoplasm. The nucleus is slightly stained with scattered chromaffin granules and nucleoli which are not distinguishable or are hardly so.

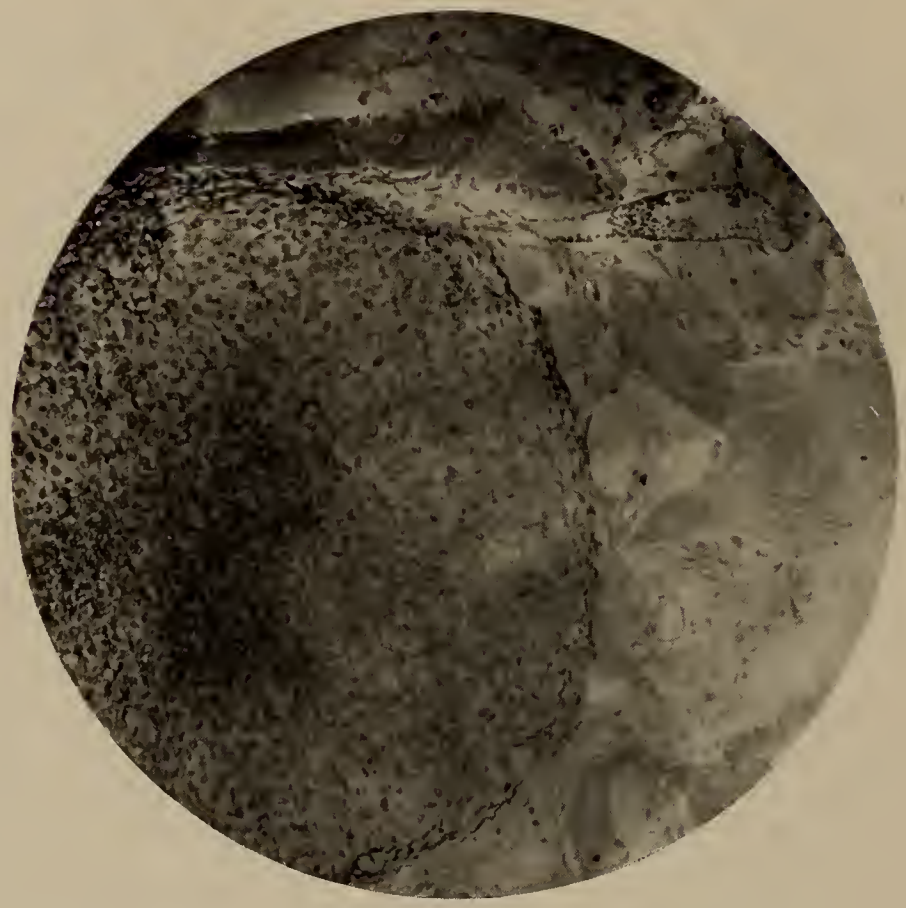


Fig. 60. Case 267. Ewing's sarcoma. Showing hydropic degeneration of the tumor cells.

The cytoplasm frequently simulates a syncytium. While mitoses are abundant it is a striking feature that no tumor giant cells are seen here, the cells containing a single nucleus. The cells are extremely uniform, no pleomorphism being observed. The arrangement of the tumor cells is peculiar. Coherent pavement sheets of cells without any definite structure formation in the various sized lobules is the most frequent finding (Fig. 59). Not infrequently one encounters mucoid or hydropic degeneration of the tumor cells (Fig. 60). Complete necrosis with liquefaction is not uncommon. Frequently in section the cells are seen so close to one another as to influence the shape of the cell. A not uncommon finding is the arrangement of tumor cells about blood vessels, arterioles and capillaries (Fig. 61). An opinion has even been ventured that the blood vessels present a structural unit of Ewing's sarcoma. While the tumor cells sometimes appear arranged like a mantle about cross sections of blood capillaries, there is no evidence to support the view that, in this, Ewing's sarcoma differs from other cellular sarcomata with the so-called perithelial or perivascular arrangement. Disintegration of the tumor cells far from blood vessels leads to this appearance in any rapidly growing cellular tumor. The so-called perithelial arrangement is therefore not a necessary sign of Ewing's sarcoma, although a common one.

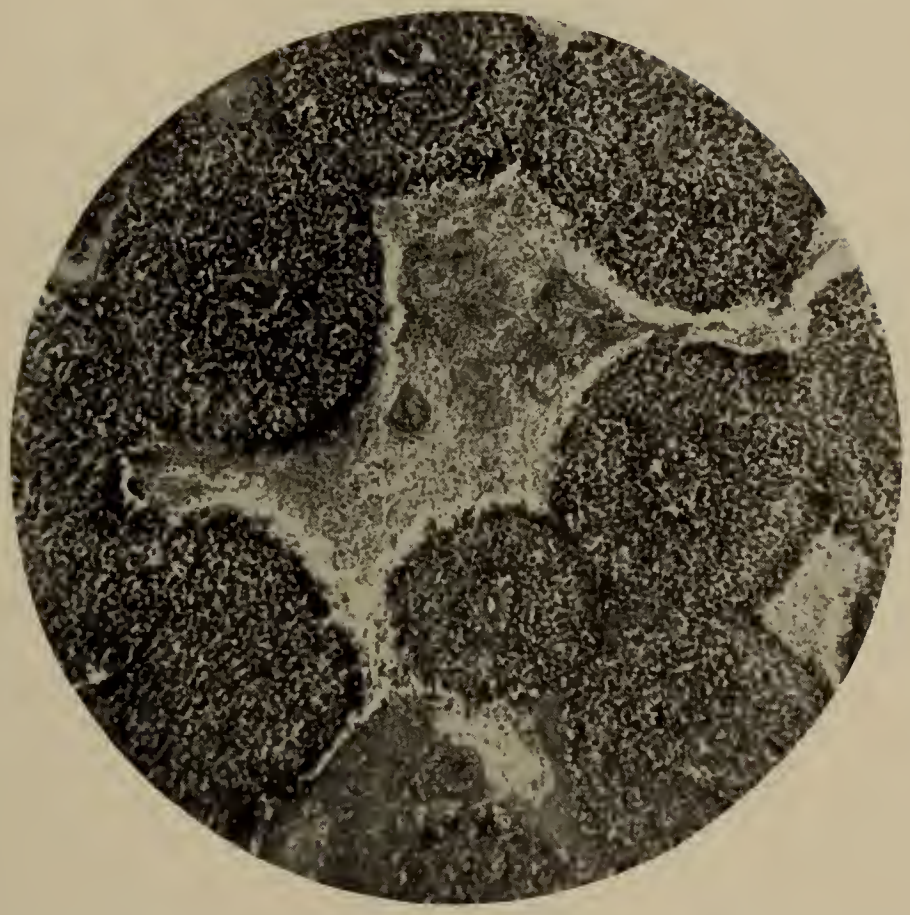


Fig. 61. Case 364. Ewing's sarcoma. Arrangement of tumor cells about arterioles and capillaries.

A striking feature of Ewing's sarcoma is the complete absence of intercellular substance. The syncytial stainless cytoplasm of the tumor cells occasionally leads one to an erroneous conclusion that the cells are embedded in an intercellular substance, but no definite cell borders can be made out there. This syncytium caused observers to suggest œdema of the tumor cells; however, the same occurrence is seen in well fixed Zenker preparations. In some spots thrombi of agglutinated red cells, and eosin staining globuli simulate intercellular matrix. Another source of error as to the presence of intercellular substance arises in connection with the hyalinized blood vessel walls supplying the tumor. Usually the eosin stained homogeneous ring of the cross section of the blood vessel wall separates the tumor cells packed around it from the lumen filled with intact blood and lined with normal endothelium (Fig. 62). In tangential longitudinal sections the blood vessel wall will readily form trabeculæ of hyalinized homogeneous connective tissue lined with rows of tumor cells (Fig. 63). These homogeneous rings and strips have been erroneously interpreted as an intercellular substance of the tumor cells. In reality these collagen fibers are not produced by the tumor cells. The tumor cells in Ewing's sarcoma do not produce anything;

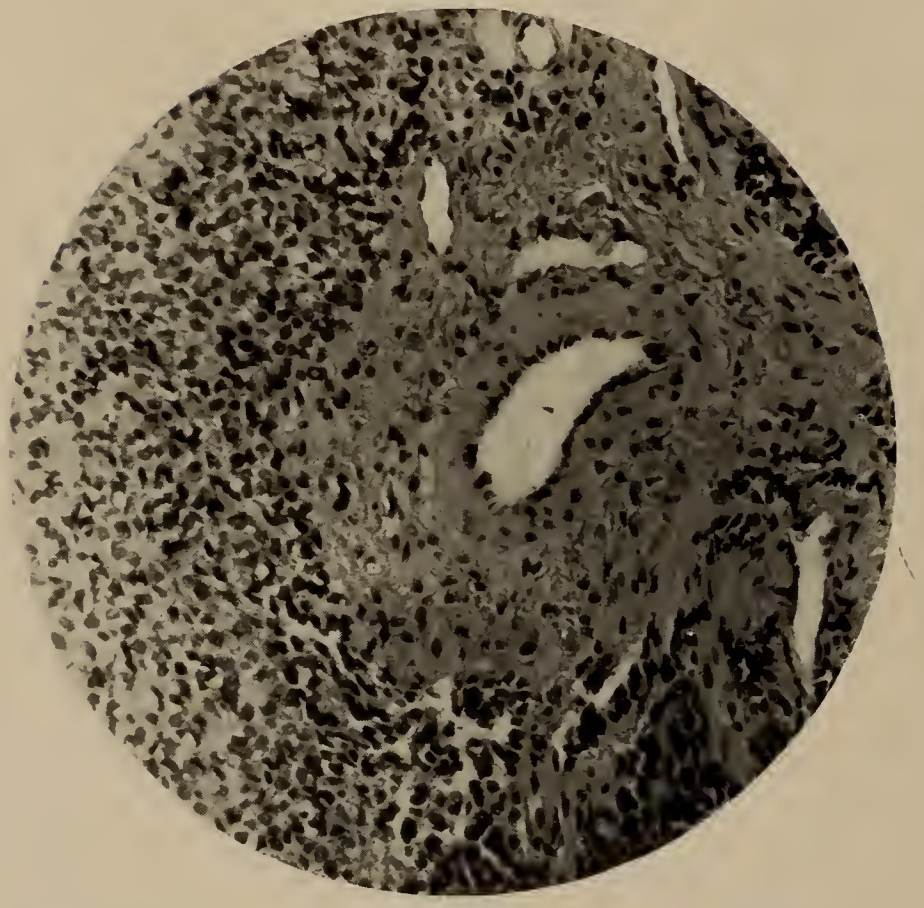


Fig. 62. Case 515. Same tumor as that in Figure 63. A homogeneous ring in the cross section of the wall of the blood vessel separates the tumor cells from the lumen of the blood channel.

in this respect they seem to be far more primitive than the tumor cells in osteogenic sarcoma, if indeed any analogy may be drawn between them.

The histological picture of Ewing's sarcoma is somewhat complicated by the reaction of the tumor on the osseous tissue of the affected bone. As pointed out above, diffuse bone absorption is one of the characteristic features of Ewing's sarcoma. The extensive absorption of the shaft is accomplished without the help of giant cells. In sections one frequently sees bone trabeculæ with typical morphological features of necrotic bone closely surrounded by tumor cells. The new formed bone is of both neoplastic and metaplastic variety. Along with areas of well formed lamellary bone close to the periosteum one encounters islands of new formed bone of low grade quality in the neighborhood of the tumor cells (Fig. 64). Since the tumor cells in Ewing's sarcoma do not form any intercellular substance, this bone is doubtless a product of a regenerative process of the affected bone. This is another proof that the distinction between well formed lamellary reactive bone and trabeculated low grade tumor bone is unsound.

The typical histological structure of Ewing's sarcoma is not infrequently accompanied by peculiarities which are apt to complicate it somewhat. To these

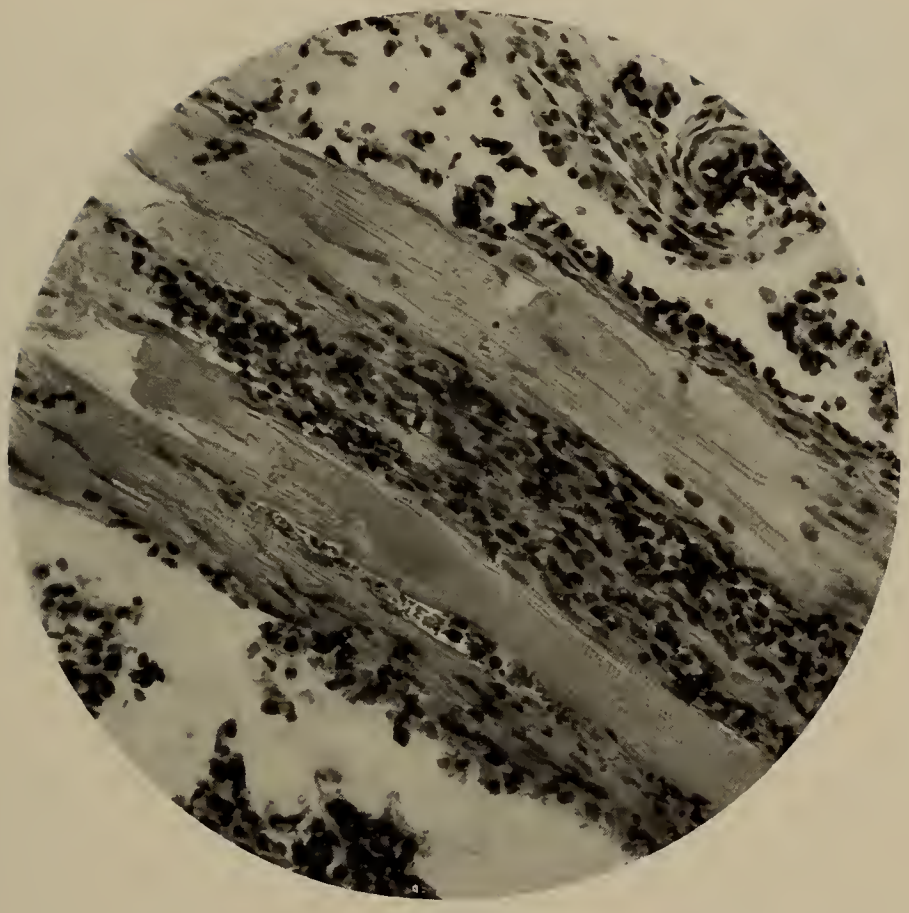


Fig. 63. Case 515. Compare with Figure 62. Ewing's sarcoma. Showing a tangential section of the wall of a blood vessel surrounded by tumor cells. Notice the trabeculæ of the hyalinized homogeneous connective tissue of the wall.

belongs the admixture of plasma cells. This fact suggests the question of the relationship between Ewing's sarcoma and a plasma cell myeloma, a question which must be left in abeyance because of our present lack of knowledge of the origin of myelomata in general. A generous admixture of blood cells and bone marrow elements may still further complicate the appearance. As in osteogenic sarcoma one meets in Ewing's sarcoma also with an occasional lymphocytic infiltration. This infiltration when present is usually observed in the peripheral portions of the tumor where tumor frequently appears to consist of tissue truly indistinguishable from inflammation in the bone. Because this reaction is especially marked in the periphery of the tumor, one readily understands how an exploration here will lead to an erroneous diagnosis of inflammation. The admixture of these numerous cellular elements to the tumor cells often so complicates the picture that the tissue, after passing through poor technical preparations, is difficult to distinguish from myeloma or inflammatory lesions of bone.

Generalization of Ewing's sarcoma with metastatic growths elsewhere in the body proceeds through the blood and lymph stream, favoring the lymph stream

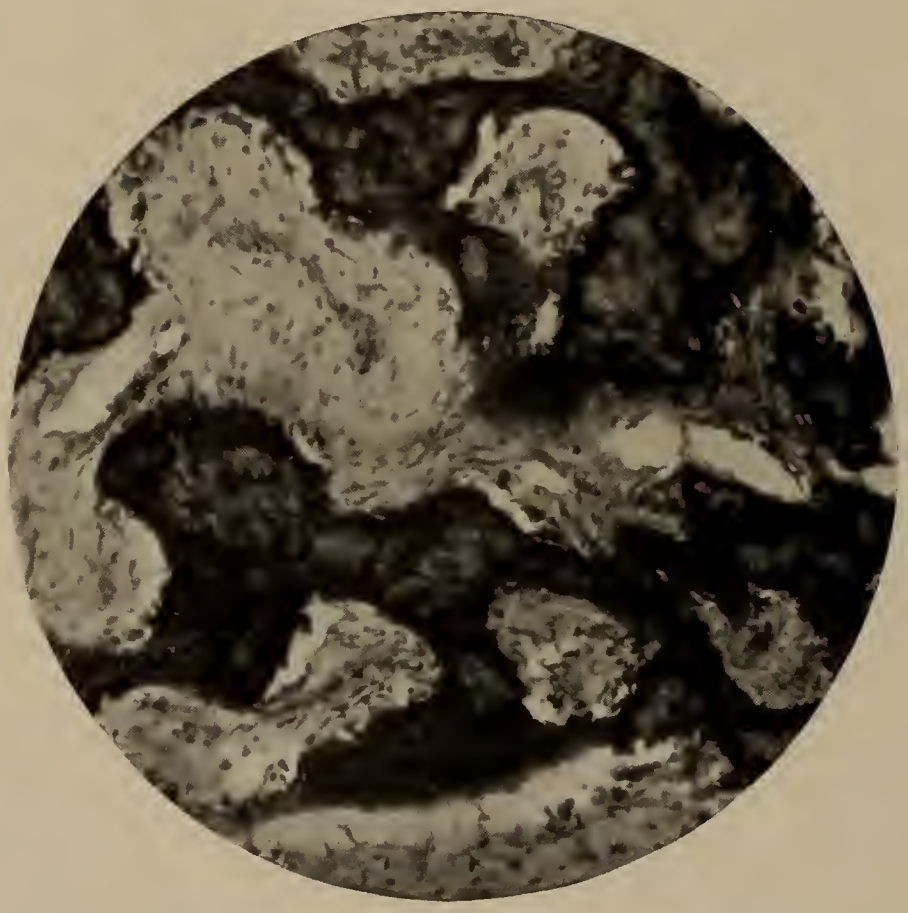


Fig. 64. Case 292. Ewing's sarcoma. Low-grade newly formed bone is seen in the close proximity of tumor cells.

more frequently than osteogenic sarcoma. Metastatic involvement of regional lymph nodes in Ewing's sarcoma is not infrequent. Unlike osteogenic sarcoma, Ewing's sarcoma is apt to metastasize to other bones of the skeleton and especially to the skull. The lungs and skull with the scalp are the most frequent seats of a metastatic Ewing's sarcoma. The metastatic foci in bone repeat all the characteristic features of Ewing's sarcoma and especially the diffuse bone absorption. The solid cellular growths occurring in skeletal and pulmonary metastases show a greater tendency to regressive changes than is the case in osteogenic sarcoma. While occasional calcification of a degenerated area in a metastatic focus has been observed, true bone formation does not occur in metastases of Ewing's sarcoma. This fact is also important proof that the origin and the physiology of the tumor cell in Ewing's sarcoma is at great variance with that of osteogenic sarcoma.

There has been noticed an attempt on the part of men defending Ewing's viewpoint of the endothelial nature of Ewing's sarcoma (Connor) to subdivide this tumor into various types. They based this subdivision upon the relation of the groups of tumor cells to the adjoining blood vessels. They describe angio-endothelioma as a variety of Ewing's sarcoma, when the tumor cells become

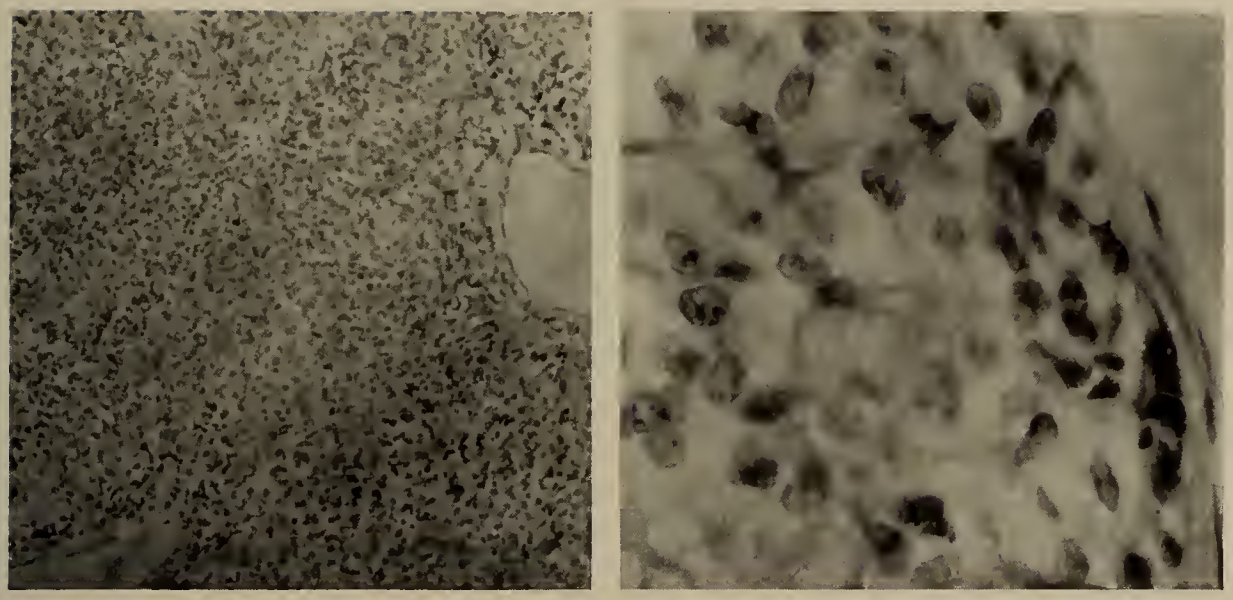


Plate 24. Case 326. Ewing's sarcoma. Showing the normal endothelium lining the blood channels surrounded by tumor cells. Low and high magnification.

flattened approaching the normal vascular endothelium and forming blood vessels and sinuses and showing a perithelial arrangement. That the so-called perithelial arrangement is not a specific feature of Ewing's sarcoma and is not infrequently observed in any rapidly growing cellular tumor has been previously stated. The presence of blood in spaces between tumor cells is no evidence that these tumor cells have been acting as a vascular unit; it is too well known with what ease a hæmorrhage may take place in a loosely arranged conglomeration of tumor cells. The attempt to interpret the tumor cells surrounding the blood cells as a vascular lining is in extreme discord with repeated statements of Ewing himself that the vascular endothelium has no relation to the origin of Ewing's sarcoma (Plate 24). An angio-endothelioma is a tumor of the vascular endothelium. It is characterized by the large cuboidal or cylindrical cells with clear cytoplasm and sharp cell membrane which constitute it. The clear cut difference between these cells and the type cell in Ewing's sarcoma is obvious. Ewing distinctly discriminates between angio-endothelioma of bone and the diffuse endothelioma (Ewing's sarcoma). Not only the histology but also the clinical behavior, the roentgenological picture and the prognosis of angio-endothelioma is different from Ewing's sarcoma. There can be no doubt that such a confusion of angio-endothelioma with Ewing's sarcoma is against all the present knowledge and evidence on hand and is misleading.

A most interesting point in the pathology of Ewing's sarcoma is the question of the origin of the tumor. While almost all who have had the opportunity to study the collection of Ewing's sarcomata in the Registry material agree that this is a specific disease, not all are willing to accept Ewing's contention that the tumor originates from the perivascular endothelium. As in any other rapidly

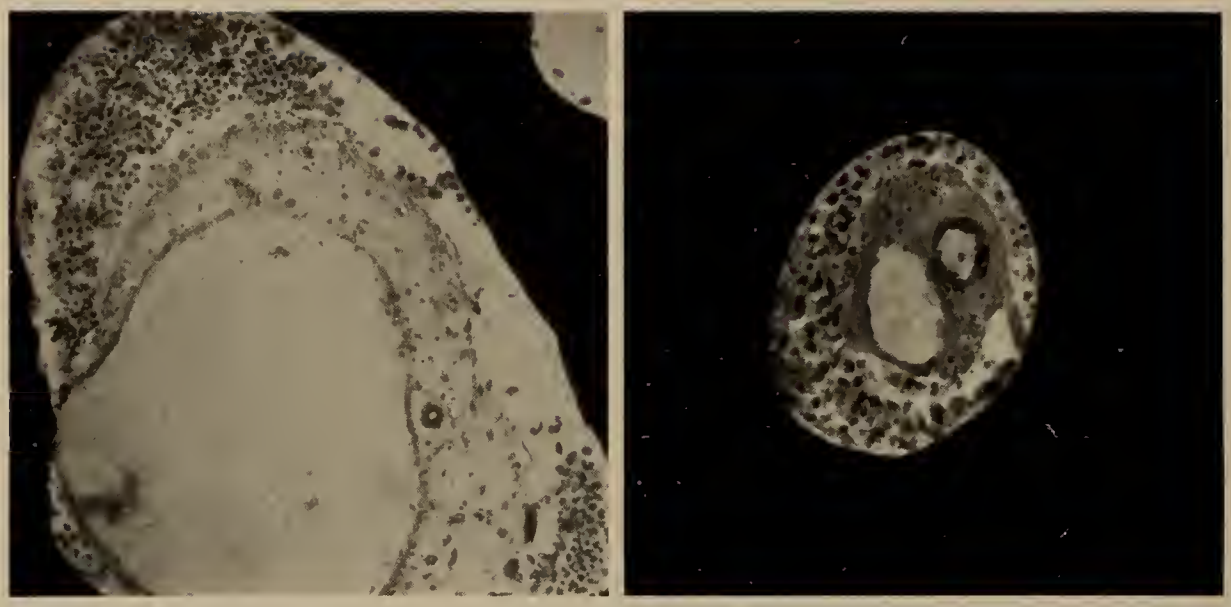


Plate 25. Case 418. Same case as that in Figure 68. Ewing's sarcoma. Minute foci of tumor cells arranged perivascularly in the haversian canals.

growing malignant tumor it is difficult to arrive at a conclusion about the origin of the tumor in the more or less advanced stages of growth, from observation alone. In the Registry material cases of Ewing's sarcoma are encountered in various stages of growth and those in the very early lesions may suggest the possible origin of the tumor. In one or two of these tumors in early growth one finds in the periphery a sprinkling of minute foci of tumor cells arranged perivascularly in the haversian canals (Plate 25). The normal presence here of perivascular lymphatics and vasa vasorum would seem to suggest that the cells originated about these anatomical structures. The nearer they are to the main tumor mass, the larger and the more numerous the foci become, and finally they merge with the main tumor mass. Whether these accumulations of tumor cells originate in the spaces where they seem to lie or whether they are brought here in the lymphatics from the main tumor, is a subject for speculation. The nature and the origin of these cells cannot be asserted positively even in these locations seemingly most favorable for study. Ewing feels that the cells of Ewing's sarcoma are "to be assigned to some endothelial category, and it may be that the interpretation of 'endothelium' may have to be widened to include this group. I do not think they arise from blood or vascular endothelium. They may possibly arise from perivascular lymphatic endothelium.[1]" Considerable argumentation of purely hypothetical character was brought in support of Ewing's hypothesis of the endothelial origin of Ewing's sarcoma. However, all these considerations are both questionable and unavailing in the absence of sufficient evidence in favor of this hypothesis. The difficulties in deciding this question of origin are great. One doubts whether morphological studies alone will ever successfully

[1]Ewing, James. Endothelial myeloma of bone. Proc. New York Path. Soc., 1924, xxiv, 93.

solve this problem. As in other tumors the essential experimental link in the chain of evidence is lacking here.

The clinical and pathological concept of the disease invites some theoretical speculations. In the face of the evidence accumulated from our study of this condition one is justified in expressing a suggestion of the probable constitutional nature of this disease. The relation of Ewing's sarcoma to lymphogenous disturbances is very suggestive. In this respect it is of significance that on the outskirts of Ewing's sarcoma there is evident an absence of blood forming elements in the bone-marrow. That Ewing's sarcoma is more than a simple bone tumor is evidenced by the diffuseness of involvement and the multiplicity of foci of origin in the same bone and also by the appearance of multiple tumors frequently very early in the course of the disease. One rarely sees a malignant tumor where the primary and secondary involvement appear almost simultaneously.

Clinical Course

The history and the clinical course of cases of Ewing's sarcoma are characteristic enough to allow a distinction between them and other bone tumors and are of great importance in the diagnosis of this disease. This fact is not yet appreciated and, as in osteogenic sarcoma, the clinical history is not given the deserved interest and attention.

The clinical incidence and frequency of Ewing's sarcoma may be judged from the fact that in a series of about 650 cases of bone tumor which have been submitted to the Registry as "bone-sarcoma" there were 40 instances of Ewing's sarcoma. If to these 40 cases one adds 10 others of more or less doubtful nature, but greatly resembling Ewing's sarcoma, one obtains the frequency of Ewing's sarcoma as 7.5 per cent of all instances diagnosed by the average operating surgeon as "bone sarcoma." In Ewing's sarcoma the male sex distinctly predominates, there being about three times as many males affected as females. In this respect Ewing's sarcoma resembles also skeletal myeloma which affects decidedly more frequently males than females. Ewing's sarcoma differs from myeloma and approaches clinically osteogenic sarcoma by the age incidence. While myeloma is encountered mostly in the fourth and fifth decades, Ewing's sarcoma falls in the last half of the first and the first half of the second decade of life. Of 40 typical Ewing's sarcomata in the Registry material 20 cases were observed in patients of the age between 6 and 15 years and only 3 cases after the age of 40. It is of interest to note that among the patients with Ewing's sarcoma some are very delicately built with slim graceful long bones, while others are fat with evidence of endocrine disturbances.

Ewing's sarcoma differs greatly from osteogenic sarcoma in location. The long pipe bones are the favored seat of the disease, but the most frequently involved bone is the tibia, next in frequency are the fibula, humerus, ulna, and

then the femur. In distinction from osteogenic sarcoma Ewing's sarcoma is a not uncommon affection of the clavicle, of the small bones of the feet, the ribs, vertebræ, mandible, and skull. The bones of the shoulder girdle and of the pelvis are all represented among these cases. The most striking feature of Ewing's sarcoma is that the site of predilection is the shaft and not the epiphyseal ends of the long bone. The involvement extends over a wide area usually more than half the length of the bone and occasionally an involvement of the entire shaft is encountered. Apparently the epiphyseal ends of a long bone are not absolutely immune to Ewing's sarcoma and occasionally one sees a Ewing's sarcoma affect the end of the bone. However a Ewing's sarcoma never proceeds as close to the end of the bone as does an osteogenic sarcoma. When a Ewing's sarcoma affects the spine, more than one vertebra is usually involved. The fact that the involved vertebræ are usually adjoining one another would seem to remove all possible doubt as to whether the involvement of all vertebræ is primary or whether some are metastases from the primary. This question of whether a multiple Ewing's sarcoma represents a true multiple primary involvement or merely metastases from one primary is even of more importance in Ewing's sarcoma than in osteogenic sarcoma. As was mentioned, a simultaneous osteogenic sarcoma of more than one bone is a curiosity, while in Ewing's sarcoma this is rather a characteristic feature of the disease (Plate 26). In the advanced stage most cases of Ewing's sarcoma reveal multiple lesions in the skeleton. Such tumors occur almost constantly in the skull and frequently in the extremities and ribs. This question is obviously of significance because of therapeutic considerations, since if the tumors are multiple there is a contra-indication to amputation while if they are metastases there is a vital indication for early aggressive radical treatment. It would seem that the extensive occurrence of skeletal tumors in advanced stages of a Ewing's sarcoma with the relative integrity of other organs points to the probability that the tumors are truly multiple and not skeletal metastases.

A frequent point in the patient's history is previous trauma at or near the seat of the tumor. The significance of trauma as an etiological factor in Ewing's sarcoma is open to the same speculations and objections as in osteogenic sarcoma, however in Ewing's sarcoma the history of trauma combined with the complaints of pain and fever, as described above, sidetracks the physician toward an erroneous diagnosis of osteomyelitis. Pain is an important and constant component of the patient's history. In distinction from pain in osteogenic sarcoma pain in Ewing's sarcoma is of a more intermittent character. Frequently the incipient pain after the trauma subsides, and the injury is entirely forgotten until an attack of sharp pain in the affected region combined with a febrile reaction reminds the patient of the trauma. The incipient attack lasts a few days and several months may pass before another attack occurs, while any

Plate 26. Case 385. Same case as that in Plate 27 and Figure 58. Ewing's sarcoma in a boy 8 years old. Death 18 months after the onset. A diffuse involvement of most of the bones of the skeleton. The tumor first arose in the left os calcis. Notice the grossly intact outline of the femur while the medullary cavity is extensively involved.

localizing symptoms may be completely absent. Each succeeding attack is of longer duration and of greater severity, and the intervals between the attacks constantly grow shorter, until finally the pain becomes of a permanent rheumatoid character. Usually at this stage a distinct tumor growth is recognized on palpation. It is not unusual to see a patient with Ewing's sarcoma up and around for more than a year, suffering from intermittent pain and attacks, before being confined to his bed. The fever accompanying the attacks may be of considerable severity. The febrile attacks throughout the course of the disease suggests that the tumor is essentially a lesion of the bone-marrow. The blood findings are of very little significance; however, not infreqeuntly it also points toward an inflammatory disturbance. The leucocytes may number 12,000 to 15,000, maintaining the normal relationship in the differential count. In far advanced cases a typical picture of secondary anæmia is present. It is easy to see how repeated attacks of fever and pain some months before tumefaction is revealed, all preceded by a trauma, lead the physician to an erroneous diagnosis of osteomyelitis. Frequently a patient with Ewing's sarcoma is operated on under a diagnosis of osteomyelitis, some are even operated on repeatedly with this diagnosis, which is also suggested by the pathologist's report of the examination of the tissue removed.

The skin overlying the bone remains free from involvement save in rare instances in far advanced stages of the disease. A surgical exploration of the tumor usually leads to a continuous ulceration with large fungous growths protruding through the incision. However a healed exploratory wound is not to be looked upon as a point against a malignant tumor since complete or temporary healing of such exploratory incisions do occur. Palpation is an important aid in the diagnosis of Ewing's sarcoma. Palpation allows one to determine the general outline of the tumor, its wide extension along the involved bone and its consistency. Repeated palpation is of primary importance when radiation is used as a diagnostic therapeutic test; one is surprised how easily the changes in outline, size and consistency of a Ewing's sarcoma subjected to radiation therapy can be perceived by palpation. Palpation may early reveal the response of the regional lymph nodes to the disease. An enlargement of the regional lymph nodes here is of even more significance than in osteogenic sarcoma, since here this is frequently not only an inflammatory enlargement but a true metastatic involvement.

The first appearance of the tumor and its further progress are rather peculiar. As mentioned above, the first febrile attacks are of more general constitutional character and no localizing is present. The tumefaction arises suddenly with signs of local hyperæmia and inflammation. After the febrile attack and most symptoms of general malaise subside, a tumor is discovered. At commencement the tumor may be slow in progress; it may also entirely subside and disappear,

merely to return with a subsequent attack in a considerably larger size. Then the growth becomes continuous and increases rapidly in size before the termination. The incipient temporary variations in size of the tumor often lead the patient and not uncommonly also the physician to an erroneous conclusion of a spontaneous cure. The patient keeps up his daily work until a new attack finally leads to a persistent tumor. Pathological fractures are not typical of Ewing's sarcoma, save in the terminal stage of the disease. Joint involvement is unknown in Ewing's sarcoma for obvious reasons: that the shaft is involved instead of the ends of the bone and that Ewing's sarcoma does not proceed to the articular cartilage.

The terminal stage of Ewing's sarcoma is different from that in osteogenic sarcoma, although it is necessary to admit that our knowledge of the final stage of the disease is much less accurate. As a general rule the patient is taken home before termination where he remains until death; necropsies of such patients are scarce. The generalization period cannot be set accurately since metastases are apt to show up on one hand in such a short interval of time as a few months after the appearance of the primary lesion, and on the other hand years may pass before metastases are found. The advent of metastases is frequently accompanied by severe febrile disturbances, especially in pulmonary involvement. Frequently the first organ to show a metastatic involvement is the skull. After the appearance of the first secondary tumor, the disease may again become stationary for some period of time especially after radiation. Months or even a year may pass before pulmonary metastases reveal themselves and secondary tumors in other bones appear. The patients are usually greatly emaciated at this stage of the disease and soon die. Metastases to the regional lymph nodes are not uncommon in Ewing's sarcoma although they are far behind the skull and the lungs in frequency. From the scarcity of evidence which it has been possible to obtain at necropsy, it seems that metastases to other soft organs are not frequent. In several cases an extensive involvement of the kidneys, liver, and spleen were observed (Plate 27).

Summarizing the average history and clinical course of a patient with Ewing's sarcoma, the most striking features are—trauma followed by intermittent pain of long duration, tumefaction, and diagnosis of osteomyelitis. When in a young person a seemingly trivial trauma is followed by an insidious onset of fever and intermittent limping due to a recurrent aching bone and is accompanied by a slight or no increase in leucocytes a tumor is more probable than is osteomyelitis. The following is a history of Case 538 of the Registry, unanimously accepted as Ewing's sarcoma. The history is a good illustration of a typical course of Ewing's sarcoma and also of the errors in diagnosis which are apt to accompany this tumor. Only by realizing how easy it is to make similar errors in this disease can such errors be avoided.

Plate 27. Case 385. See Figure 58 and Plate 26. Ewing's sarcoma. Visceral metastases.

Case 538. A boy 6 years old sustained an injury to the left leg below the knee by falling down steps. He limped and complained of pain for about a week after the accident, with fever at night. Ten days after the trauma he was seen by a physician; his temperature was 102 degrees F., pulse about 140, and leucocytosis 12,000. A roentgenological examination showed an area of absorption along the medullary canal of the tibia about 4 inches below the proximal articular end, the bone showing a definite periosteal reaction. A diagnosis of osteomyelitis was made and the patient was operated upon immediately. A hole was chiseled into the marrow cavity and a small "pus cavity" was curetted. A silver wire drain was inserted and the incision closed. The pathologist's diagnosis was "subacute osteomyelitis; pus sterile." An uneventful convalescence followed; the incision healed and the temperature dropped to normal in about 3 days. About a month later pain returned with slight fever. An examination showed the affected area in the tibia to have increased slightly in size. Nothing was done at this time. Two months later the patient was brought back with severe pain in the leg. There was localized tenderness and swelling in the neighborhood of the old operative wound. The history at this time revealed that several days previously he began to complain of soreness and pain in the leg and of fever. He walked with perceptible limp but the knee joint showed no disability. He was readmitted to the hospital with a temperature of 100 degrees F. and leucocytosis of 15,000. At this time the roentgenogram showed the absorption in the medulla and the periosteal reaction more pronounced than before (Fig. 65). A second operation was performed. Through the old incision the hole in the bone was enlarged upward toward the tibial tubercle where a "large pus pocket was found containing yellowish-red pus." The marrow cavity was curetted radically until "hard healthy bone was found on all sides, bone cavity wiped out with phenol and alcohol." The incision was again closed with a wire drain, *in situ*. The pathologist's diagnosis was "subacute osteomyelitis, agar and broth cultures of pus showed no growth."

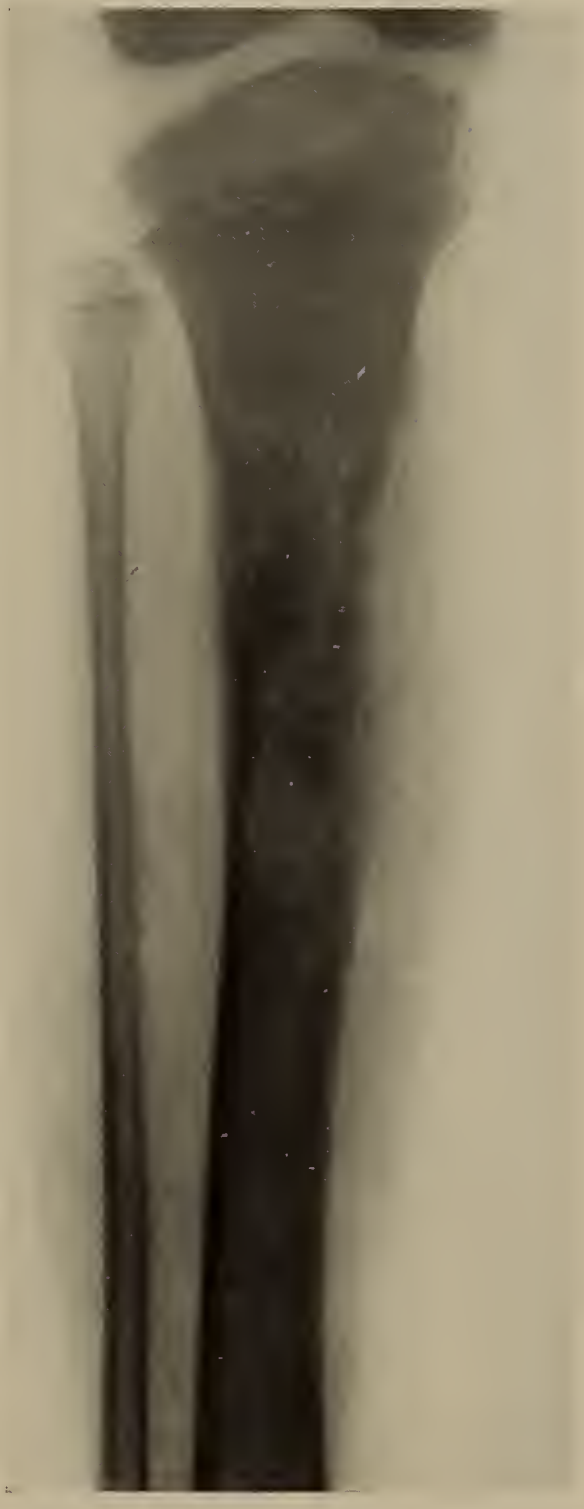


Fig. 65. Case 538. Same case as that in Plate 30. Ewing's sarcoma. The clinical history of this case is given in the text. The roentgenogram was taken before the second exploratory operation. A careful interpretation of the roentgenogram would have suggested a diagnosis of tumor at this stage while histological examination of the curettings continued to sidetrack the diagnosis for another 14 months.

About a year after the first onset of pain there was no improvement clinically in the patient's condition. The leg continued to be painful at intervals accompanied by an occasional rise in temperature. The roentgenogram at this time showed the area of destruction in the medullary canal to be about five times its size at the first operation. The neighboring bone and the medulla showed irregular deposits of calcium and an occasional area of absorption. The cortex posteriorly was partially destroyed. There was no involucrum formation. The diagnosis at this time was "osteomyelitis, probably tuberculous." Sixteen months after the first onset of pain the leg was again examined and showed no improvement clinically and a further destruction of the cortex. There was some fraying of the periosteum at the ends of the apparent involvement of the bone. Eighteen months after the first onset of pain the patient returned for roentgen-ray examination. Numerous small rarefied areas of absorption were seen throughout the bone. Plaster cast was applied. Twenty-two months after the onset of the disease the roentgenogram first raised a suspicion of malignancy. Considerable calcified material was thrown out and a soft tissue tumor surrounding the bone was seen. At this time a sinus was curetted to secure tissue for histological examination. Pathologist's report: "Typical lymphoid cell granulation tissue with one spot of tumor tissue infiltrating the granulation tissue." Following the application of a new cast a profusion of fungus-like "granulation tissue" suddenly bulged out through the window in the cast. At this time the patient was 8 years old, the duration of the illness being 2 years; he was running a septic temperature and suffering great pain. The hæmoglobin was 70 per cent, red cells numbered 2,600,000, leucocytes 9,000. The wound was again curetted for a histological diagnosis. The pathologist reported: "The diagnosis rests between sarcoma and granulation tissue; there are very cellular areas suspicious of sarcoma." Radiation therapy was started on the left leg, on the lungs, and on all other bones except the skull. Two weeks later the circumference of the left leg had become reduced from 30.25 centimeters to 27 centimeters. The granulations became of a healthy appearance; the temperature became normal, and the pain entirely disappeared. A month later radium treatment was given. The child's condition improved rapidly; he gained 3 pounds. Two months later "removal of large sequestrum was thought advisable." Sequestra were removed with a large quantity of necrotic soft tissue. Microscopically there was "no positive evidence of sarcoma." A month later after the last operation the child developed headaches; roentgenological examination of the skull showed numerous sarcomatous metastases; there was no indication of metastases in the lungs or ribs. Radiation therapy to the skull soon relieved the headaches and the general condition was fairly good. Treatment was continued for 3 months after the skull metastases were discovered, when the left leg again began to pain. The general condition of the child became poor, the granulation tissue had again piled up and acquired a foul odor, and the patient died 2 months later, 2 years and 10 months after the first onset of pain.

Diagnosis

In studying Ewing's sarcoma, one is especially impressed by the danger of an overestimation of the roentgenological method of examination on one hand and an exaggeration of the diagnostic possibilities of histological examination alone on the other. In all skeletal tumors but especially in Ewing's sarcoma if one attempts to base a diagnosis on the roentgenogram alone one will frequently be mistaken, but to satisfy oneself in the establishment of a diagnosis by a histological examination alone is not less erroneous. Only a well-planned and carefully conducted analysis of the history and clinical picture together with a study

of the findings of the radiological and pathological examination will reduce *ad minimum* the errors in diagnosis. In the presence of Ewing's sarcoma the clinical history and findings as outlined above will frequently suggest the diagnosis. Among the salient features in the clinical history of the disease, trauma has a definite place. Whatever the true causative relation of trauma to Ewing's sarcoma may be it is significant for diagnosis that trauma is commonly present in the history. Next in succession to trauma are the intermittent symptoms, with apparent complete disappearance of trouble merely to return in a more severe form.

As a rule the periodically aching bone, historically following after a trauma, together with a general constitutional response, leads to a diagnosis of osteomyelitis. This error is so frequent that it is in itself a characteristic feature of Ewing's sarcoma. The findings of the subsequent early radiological examination are not incompatible with osteomyelitis. This diagnosis may be supported by the gross appearance and frequently by the histological examination of "granulations" removed during an attempt at curettage and drainage of an osteomyelitic process. Finally, after the surgical intervention the intermittently progressing tumor begins to grow rapidly and soon the error in diagnosis is exposed. The fact that osteomyelitis is almost a typical error in diagnosing Ewing's sarcoma is not surprising when one realizes how much in common these two conditions have in a superficial examination. The triad of clinical symptoms of Ewing's sarcoma, the history of trauma, intermittent pain in a bone, and the signs of inflammation greatly resemble the triad of osteomyelitis,—intermittent boils, trauma, and pain in the bone. The slow progress of the disease and the usually not very prominent constitutional reaction suggest a chronic, slowly proceeding osteomyelitis; an acute inflammation is rarely considered. In this respect Ewing's sarcoma differs from osteogenic sarcoma when an acute or subacute osteomyelitis is not infrequently erroneously considered. The not uncommon sudden onset of pain in osteogenic sarcoma accompanied as it may be by inflammation of the skin, fluctuation or pseudofluctuation and fever is a satisfactory explanation of this divergence between Ewing's sarcoma and osteogenic sarcoma. The frequency of mistaking a malignant bone tumor for osteomyelitis suggests that no diagnosis of a chronic inflammatory skeletal process should be made before the probability of a malignant tumor is considered and ruled out. On the other hand it is not unusual to observe an erroneous consideration of osteomyelitis as Ewing's sarcoma or osteogenic sarcoma. Cases are known in which radical surgery led to amputation of a limb because of such mistaking of osteomyelitis for a malignant tumor. Such errors were more frequent before modern diagnostic radiology was known. Especially suspicious in its resemblance to osteolytic osteogenic sarcoma is a central osteomyelitic abscess, so-called Brodie's abscess; its usual location in the metaphysis is not incompatible

Plate 28. (1) Normal spine, (2) metastases of a carcinoma of the breast, (3) myeloma of the spine.

with osteogenic sarcoma. However in the roentgenogram it differs from osteogenic sarcoma in the sclerosing osteitis and periostitis surrounding the lesion, features absent in osteogenic sarcoma.

A tuberculous skeletal involvement is considered chiefly in tumors of the spine. Here mostly Ewing's sarcoma is concerned, because of the favorite seat of Ewing's sarcoma in the vertebræ. A careful analysis of the clinical findings will greatly help a differentiation. Thus sensory and motor disturbances are a much earlier complication in Ewing's sarcoma than in tuberculous spondylitis. The absence of cold abscesses in advanced stages of the disease also speaks for tumor. Another differentiating point has been described in the literature: Œdema of the soft tissues overlying a vertebra which is the seat of a malignant tumor. Most important for the differentiation is the roentgenogram. It should be realized, however, that it will be disappointing to expect findings which would warrant a diagnosis from a large film where most of the spine is exposed. The suspected area of the spine, not more than 3 to 5 vertebræ, should be exposed on one film so that they all lie in the direction of the central rays.

Experience has shown that interpretation of roentgenograms of the spine are little understood by the average clinician; the fundamentals of the normal appearance of the spine in the roentgenogram are not generally known. In a roentgenogram of a normal vertebra one notices two systems of bone trabeculæ

which intersect perpendicularly and which are interrupted in their continuity by a sagittal canal carrying the main central vein of the vertebra. Most important is the fact that the height of each caudally following vertebra is larger than, or at least of the same size as, that of the one above it. A longitudinal diameter of a vertebra shorter than the corresponding diameter of the vertebra above it is to be considered as absolute indication of a pathological involvement of the vertebra. It is hardly necessary to say that the integrity of the sharpness of the outline and the uniformity of the density of a vertebra is as important diagnostically as in any other bone (Plate 28).

An important clinical symptom frequently neglected by the physician is sciatica. Sciatica may be the first symptom in tumors of the lumbar and sacral spine and the bones of the pelvis. It is also encountered occasionally in tumors of the cord as well as tumors of the soft organs of the pelvis. It is significant that with an increase of the experience of the surgeon the incidence of idiopathic sciatica decreases.

The differentiation of Ewing's sarcoma from osteogenic sarcoma is accompanied with difficulties. Much reliance can be placed upon the clinical history and course, but the roentgenogram is frequently so characteristic in Ewing's sarcoma that it decides the diagnosis. A roentgenogram of an early Ewing's sarcoma will show a diffuse involvement of the bone; this is probably due to a diffuse origin of the tumor throughout the haversian system. Usually the diaphysis is involved and not the ends. Of 40 cases of Ewing's sarcoma,

Fig. 66. Case 267. Ewing's sarcoma in a boy 8 years old. Amputation and later application of radium to abdominal metastases (?). The patient is well 5 years after the onset. The roentgenogram was taken 5 months after the onset. The apparent widening of the shaft and the displacement of the old bone by the tumor with the extensive involvement of the shaft is typical of Ewing's sarcoma.

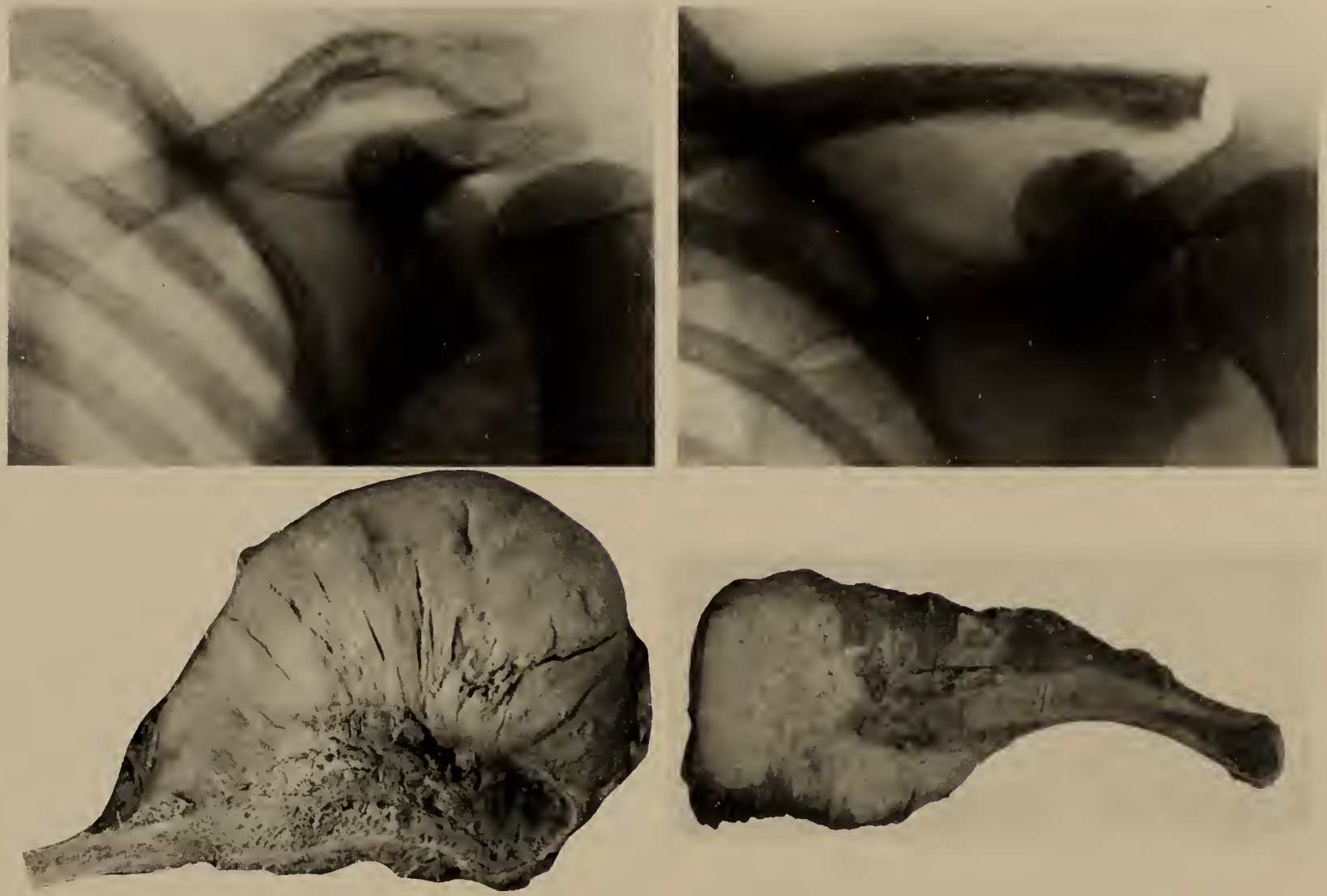


Plate 29. Cases 162 and 504. Roentgenogram and photograph of each specimen:
Lower left, osteogenic sarcoma in a girl 11 years old; 4 months after the onset. Death 11 months after the onset.
Lower right, Ewing's sarcoma in a woman 23 years old; 3 months after the onset. Death 8 months after the onset.
Showing the difference between osteogenic sarcoma and Ewing's sarcoma. In Ewing's sarcoma a destructive roughening of the periosteum is seen; the shaft of the bone is widened, while in osteogenic sarcoma the shaft with a preserved outline is passing through the tumor mass. In the photograph, Ewing's sarcoma shows a bulky fleshy soft tumor mass, while in osteogenic sarcoma the tumor mass is supported by a skeleton of radiating spicules. The periosteal spindle is well illustrated in osteogenic sarcoma.

in only two the ends of the bone were the seat of the tumor. The involvement is wide; commonly about half of the length of the bone is involved. Unlike osteogenic sarcoma which in the roentgenogram shows the shaft passing through the tumor mass grossly intact, Ewing's sarcoma shows the bone being slowly displaced by the tumor tissue (Fig. 66). The smooth absorption of the bone is accompanied by a widening of the shaft with frayed longitudinal bone trabeculæ. A destructive roughening of the periosteum is observed but there is no periosteal spindle and no lipping of the periosteum (Plate 29). The new bone is laid down parallel to the shaft; only in 3 cases out of 40 a radiating arrangement of new bone was observed (Figs. 67 and 68). In macerated and dried specimens small radiating spicules may be occasionally seen while in the roentgenogram they could not be perceived. The metastases in bone, which are typical of Ewing's sarcoma, have an appearance similar to the primary growth in the roentgenogram. A differentiation between Ewing's sarcoma and metastatic growths will be easily made if one remembers that metastases occur in the very young or after the age of 40, while most Ewing's sarcomata are seen in early adolescence.

In Ewing's sarcoma the pathological examination of tissue removed at biopsies is less reliable than in osteogenic sarcoma. If, in osteogenic sarcoma, tissue obtained through biopsies is not representative enough to allow a correct diagnosis, even more is this the case with Ewing's sarcoma. Also the fallacies of technical procedure are such that one rarely encounters a well prepared histological section which would warrant a diagnosis for the pathologist non-expert in bone tumors. There are numerous examples of the pathologist supporting the erroneous diagnosis made clinically and roentgenologically of osteomyelitis in the presence of Ewing's sarcoma. On the other hand it is fully attested at present that no other skeletal lesion so rapidly responds to radiation as Ewing's sarcoma. The suppression of Ewing's sarcoma by radiation is so marked that it in itself presents a most valuable diagnostic point in this disease. Viewed largely, the diagnostic limitations of pathology combined with the dangers of exploratory incision in Ewing's sarcoma require that a therapeutic radiation test should be substituted for exploratory incisions in cases suspected of Ewing's sarcoma (Plate 30). The intermittent symptoms, the characteristic roentgenogram, the therapeutic result will lead to a correct diagnosis.

Therapy and Prognosis

The general points of the therapy of bone sarcoma as pointed out in the chapter on osteogenic sarcoma are partly applicable also to Ewing's sarcoma. The general rapid response to radiation of Ewing's sarcoma is the main difference between this tumor and osteogenic sarcoma. Heavy radium and roentgen-ray radiation suppresses Ewing's sarcoma and causes a regression of the tumor in a short time (Plates 31 and 32). Unfortunately the enthusiasm from the first

Fig. 67. Case 541. Ewing's sarcoma in a boy of 12 years. The roentgenogram was taken 1 month after the onset of the disease. The widening of the shaft with the parallel striations is typical of Ewing's sarcoma.

Fig. 68. Case 418. Same case as that in Plate 25. Ewing's sarcoma in a boy 10 years old. Notice the radiating spicules of the new bone in the presence of all features of Ewing's sarcoma in the roentgenogram.

impression lost ground later when experience showed that the tumor, being very susceptible to physical therapy, tends to recur and slowly become refractory to further radiation. There are, however, at present on record cases of Ewing's sarcoma remaining well up to four years after the onset, in which radiation alone was used. In the material of the Registry the patients with Ewing's sarcoma lived longer who had operative treatment accompanied by radiation.

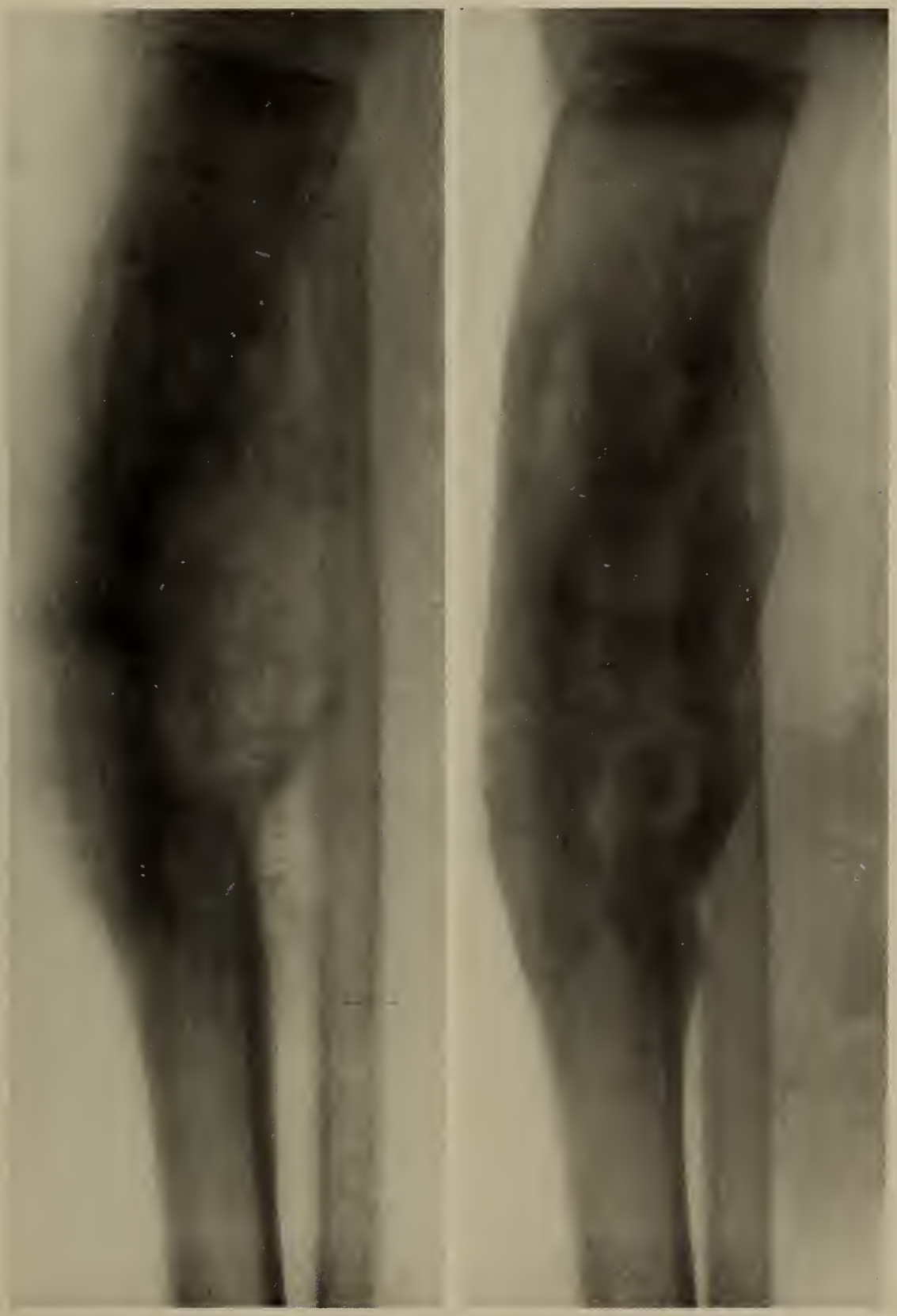


Plate 30. Case 538. The same case as that in Figure 65. Ewing's sarcoma. Showing the response to radiation therapy. Roentgenograms taken 16 months after the onset, (left) and after several exposures to roentgen rays. By a trial of radiation at a much earlier date one would have avoided in this case repeated exploratory operations.

Plate 31. Case 173. Same case as that in Figure 59. Ewing's sarcoma in a boy 16 years old. Roentgenogram taken 8 months after the onset; the leg was amputated 4 years after the onset. In the interim radium was used. Showing the temporary suppression of growth of the tumor by radiation; the gross outline of the cortex is almost completely restored.

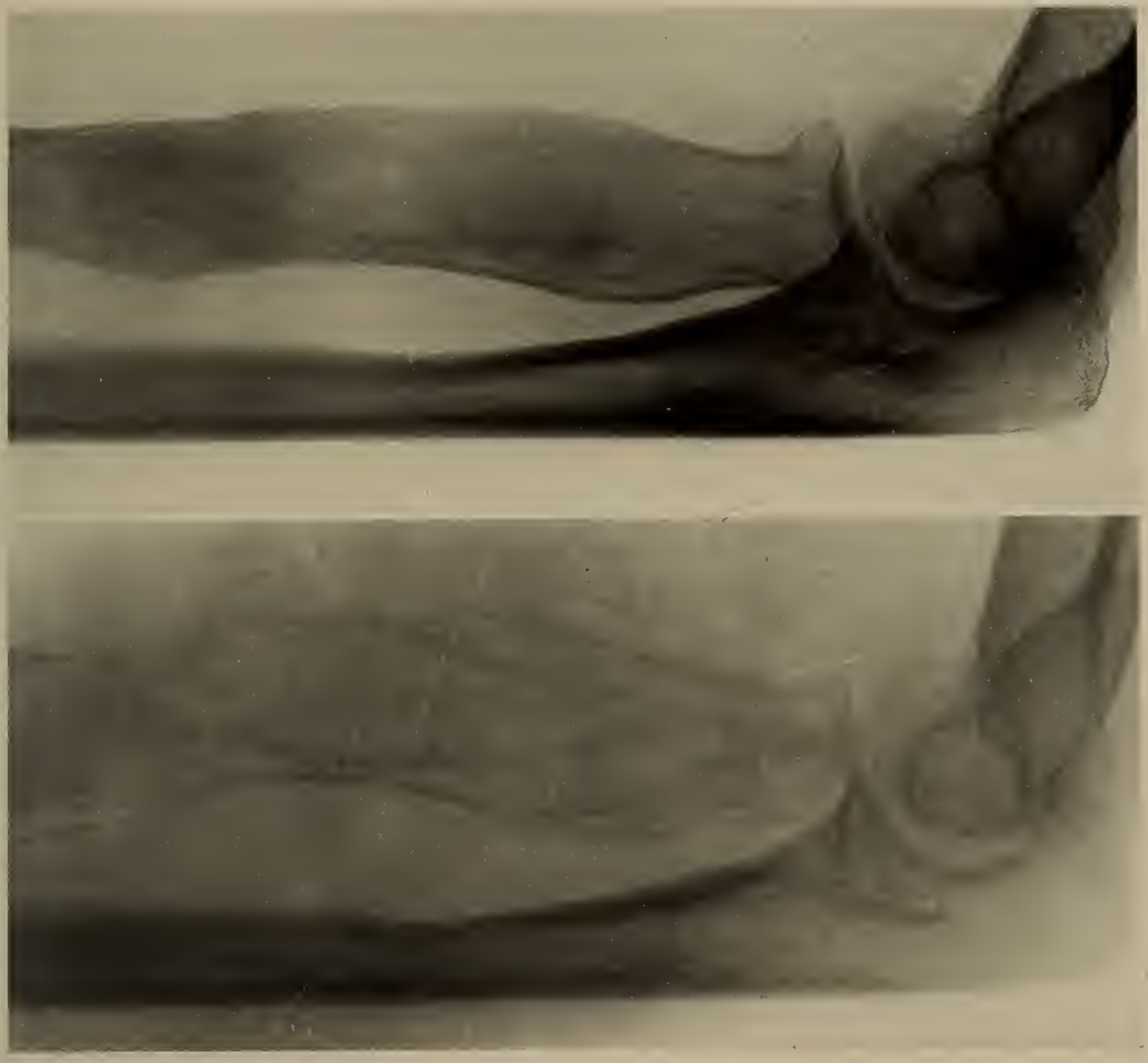


Plate 32. Case 352. Ewing's sarcoma in a girl 14 years old. An exploration was made about 1 year after the onset, at which time radium packs were applied with a good immediate local result. Death with skull metastases 3 years and 2 months after the onset.

Yet since radical surgery does not seem to prevent multiple tumors in the skeleton, amputation is possibly futile. The best way probably to deal with a Ewing's sarcoma is first immobilization of the affected region and heavy radiation; when the tumor recurs locally, then excision or even amputation can be performed. Radiation is to be continued for a longer period of time than is usually done in osteogenic sarcoma. Cases are known of the spontaneous disappearance of roentgenological evidence of pulmonary metastases for a period of years after heavy radiation. Overradiation is to be feared, since it prevents further radiation because of skin burns and because it is apt to destroy the bone produced as a result of the previous radiation. The dosage of radiation required is a matter of experience. The general impression is that radium is to be preferred to roentgen ray in Ewing's sarcoma.

As with all malignant bone tumors, prognosis as to life expectancy in Ewing's sarcoma is not possible for reasons which were pointed out elsewhere. In Ewing's sarcoma the treatment especially intimately influences the prognosis. If an average prognosis of cases with a diverse clinical course, seen in different stages of development and treated by varying methods is of any importance, then the average duration of life in Ewing's sarcoma is longer than in osteogenic sarcoma—in Ewing's sarcoma about three years while in osteogenic sarcoma about twenty months. The wide range of life duration is evidenced by the fact that one patient of the Registry cases is alive sixteen years after the onset of the disease while several patients died 5 months after the onset of the tumor.

As a disease favoring the young and adolescent Ewing's sarcoma does not show any appreciable difference in prognosis in relation to the age of the patient. There is also no evidence as yet to lead to the presumption that histological varieties of Ewing's sarcoma have anything to do with the prognosis, and the attempts made (Connor) to segregate certain varieties of these tumors probably lack clinical justification. Because of the longer life duration in Ewing's sarcoma there is greater possibility of influencing the tumor by radiation and occasional surgery, and a longer period of time in which to do it.

MYELOMA

Pathology—*Gross Anatomy*

THE voluminous and detailed descriptions in the literature of this disease are frequently based upon questionable material. As a matter of fact, myeloma is a rare condition, experienced pathologists having seen but few cases in years. Not infrequently a tumor is diagnosed as myeloma simply because of the round shape of the cells composing it. That Ewing's sarcoma is sometimes confused with and taken for myeloma I have repeatedly observed. These facts partially explain the reasons why the pathology and also the clinical course of myeloma is often being presented in different, frequently contradicting descriptions. Probably this will continue to exist until we learn more of the normal anatomy of the hæmatopoietic system in general. The numerous names offered by various investigators for the disease known today as myeloma attest the great confusion existing as to the true nature of the condition. Although myelomata are rare, they are of sufficiently frequent occurrence to warrant a consideration of this tumor in a study of primary malignant bone tumors.

In divergence with osteogenic sarcoma myelomata favor the midportions of the long bones, especially the humerus and the femur and the flat bones of the skeleton such as the sternum, ribs, skull, and the vertebræ. The tumor forms nodules ranging in size between that of a bean and that of an orange. It readily spreads along the marrow cavity, replacing the normal bone-marrow so that only on the edges of the expanding growth can one see tumor cells intermingling with normal bone-marrow elements. The tumor steadily expands in the transverse diameter of the bone. The destruction of the bone is less diffuse, is of more rapid course, and of more circumscribed character than that seen in Ewing's sarcoma. Usually no osteoclasts are assisting the tumor cells in the destruction of the bone. The cancellous bone rapidly melts down at the approach of the tumor cells. The cortical bone becomes eroded and the tumor protrudes beneath the periosteum, which is slowly undermined and pushed away from the doomed cortex. Repeatedly the periosteum forms new layers of bone in place of the thinned out or completely destroyed cortex. This new bone shell, however, rapidly melts down under the aggression of the tumor cells. As a result of this periosteal reaction the bone cortex seems expanded and the medullary cavity widened. Finally the periosteum becomes perforated here and there and the

Plate 33. Case 461. Myeloma. The medullary cavity is stuffed with tumor; pathological fracture; hæmorrhage and blood cysts.

tumor infiltrates the surrounding structures. Bending and deformity of the involved weight bearing bone may take place and spontaneous infraction or complete fracture may follow. The gross specimen usually shows a greatly thinned cortex of an expanded bone filled with an increased medullary substance, soft or firm, translucent or opaque with little or no bone trabeculæ in it. The tumor mass is gray, reddish gray, or deep red according to the vascularity. The

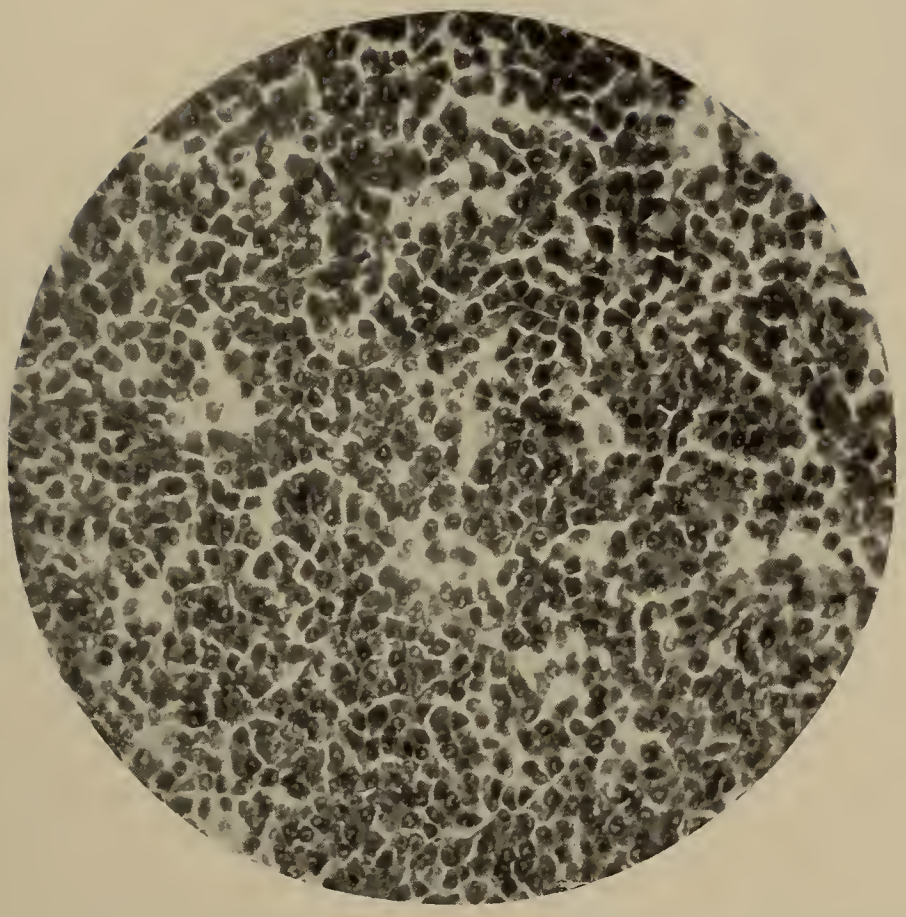


Fig. 69. Case 242. Compare with Figure 70. Myeloma, plasmocytoma. Low magnification.

vascularity is sometimes so great as to cause pulsation of the tumor. Hæmorrhage from the very thin walled capillaries is frequent; hence blood cysts and pigmentation. Extensive regressive changes are frequent with the usual changes in the cells (Plate 33).

Structure

The histogenesis of myeloma is still a field of much theorizing and speculation. Taking myelocytes, lymphocytes, and mononucleated red blood cells as the specific bone marrow cells, tumors have been described which were said to originate from each of these basic specific cellular elements. The majority of myelomata are composed of nongranulated mononuclear cells with opaque basophilic protoplasm, closely resembling the plasma cells, with which they are frequently identified. In other words the most frequent myelomata seem to be constituted by cells the origin of which is still being debated. In connection with this, it may be mentioned that an idea that all types of myeloma are composed of cells merely representing various stages of anaplasia in a single cell is being entertained. Ewing thinks that the fact that the myelocytoma is of more active growth than the plasmo cytoma, suggests that a greater degree of anaplasia may

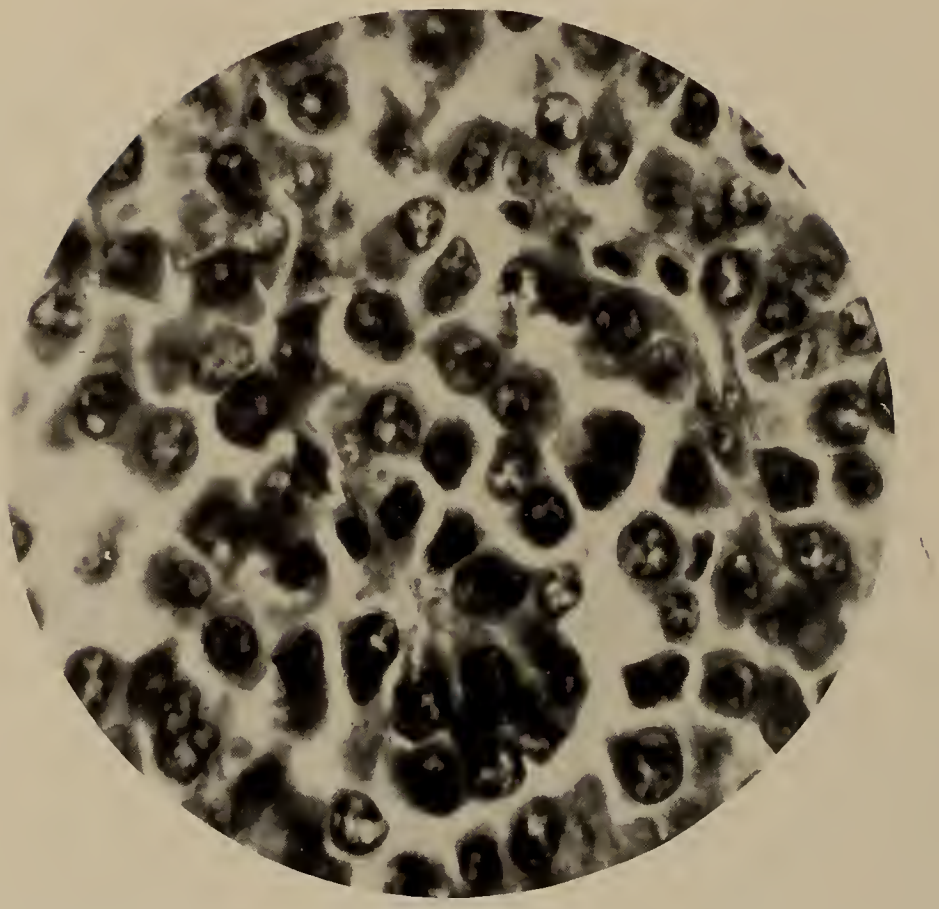


Fig. 70. Case 242. Compare with Figure 69. Plasmocytoma. High magnification.

lead a plasma cell to become a cell resembling a myelocyte. The general trend of opinion favors the origin of the plasma cell from the lymphocyte or from endothelium. According to some authors, the ability of the plasma cell myeloma to destroy bone speaks in favor of this latter alternative. Whatever the histogenesis of myeloma may be, four various types of myeloma are classified by various authors each with a different type cell and possibly with a slightly different clinical course. In order of frequency of occurrence these types are plasmocytoma, lymphocytoma, myelocytoma, and erythroblastoma. The type cell in each of these types is easily recognized in sections, but the rapidity of growth and frequent degenerative changes may obscure the appearance sufficiently to make it extremely difficult to differentiate exactly the type cell of the tumor. Among the plasmocytomata one encounters a small and large cell variety; the latter are said to be of more rapid growth and somewhat worse prognosis. The cells are usually round and oval but from pressure may become polygonal and even spindle formed (Figs. 69, 70). The nuclei are small and eccentric with granules of chromatin arranged along the nucleolar membrane. Not uncommonly the cells are multinucleated. The tumor cells are loosely packed, without any intercellular substance, without any definite arrangement and with

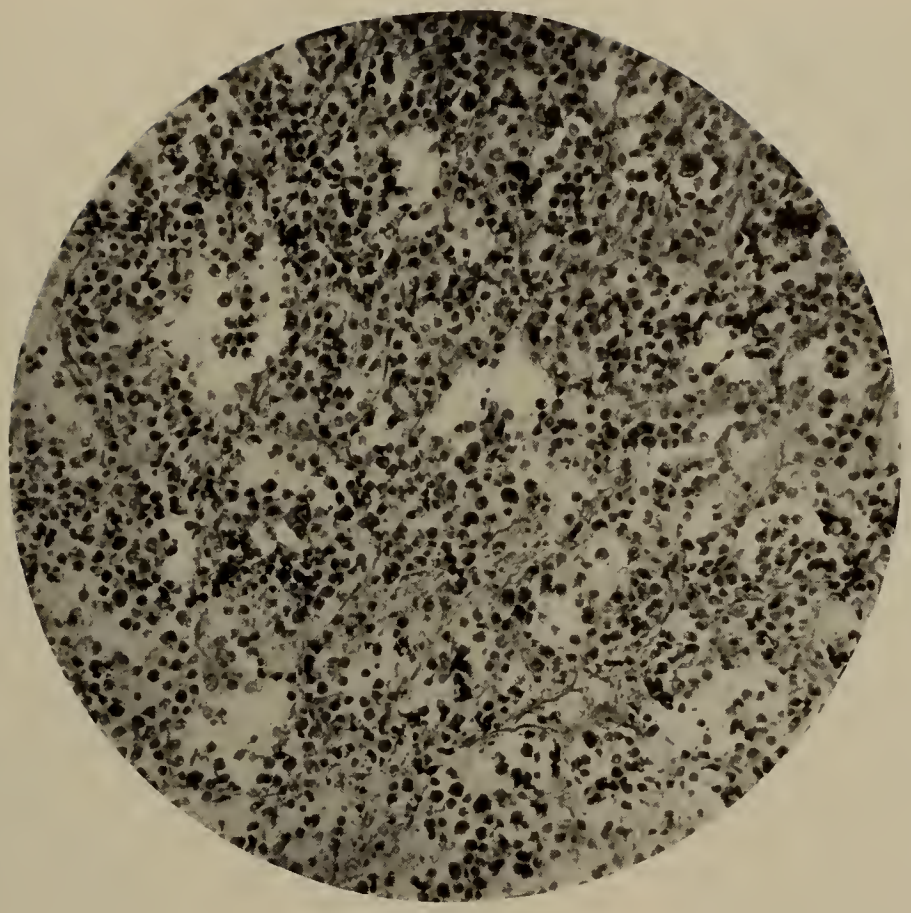


Fig. 71. Case 517. Myeloma, myelocytoma; a capillary web variety.

a scanty stroma supporting them. The lymphocytoma is less aggressive. It is composed of typical small lymphocytes. The type cell in myelocytoma resembles a myelocyte (Fig. 71). The large hyperchromatic cell with prominent granules readily suggests the myelomatous nature of the tumor. The erythroblastoma is called so because the two cases described in the literature showed hæmoglobin in the tumor cells. Hæmoglobin was so abundant that it caused a deeply brownish red color of the tumor. The Registry material is poor in myeloma, the 9 typical and 5 questionable cases registered belonging to neither of the two last mentioned types. For common use among clinicians and pathologists a subdivision of myeloma into types is probably of no advantage. Distinction of finer points in the histology of myeloma is at present of purely scientific interest.

Clinical Course

Unlike osteogenic sarcoma and Ewing's sarcoma neither the history nor the physical examination of a patient with myeloma in the early stage is in any way characteristic of the disease. This fact combined with the rare incidence of myeloma largely explains the fact that myeloma is seldom recognized before very extensive involvement takes place. The disease chiefly affects males mostly

Fig. 72. Courtesy of Dr. Holmes, Massachusetts General Hospital; not registered. Myeloma in a woman 56 years old. The same case as that in Figure 73.

between the ages of 40 and 60. Myeloma in the advanced stages extends throughout most of the bone, not infrequently replacing the entire bone marrow. For a long time it was considered a multiple lesion, originating and developing in multiple foci. Only one case of solitary myeloma was recorded.

Despite the multiplicity of myeloma in most cases the disease is connected with a traumatic history. As in other malignant bone tumors, pain is an important factor in the clinical course of myeloma, although it seems to appear considerably later than in most osteogenic sarcomata. In myeloma of the spine, cord pressure is a frequent finding. The general condition of the patient depends upon the stage of the disease; in far advanced stages a peculiar cachexia and emaciation is seen. A secondary anæmia as a result of a marked destruction of the bone marrow accompanies the cachexia. In early stages the blood may not show any changes. Cases have been described of an increase of myelocytes or plasma cells in the blood. The incipient fever is later displaced by a subnormal temperature. Palpation may sometimes reveal crepitation of the extremely thin cortex, an enlarged spleen and possibly a hyperplasia of the regional lymph nodes. The enlargement of the spleen is possibly compensatory to the destruction of the bone marrow or in the advanced stages is perhaps due to toxæmia.

Because of the rapidity of bone destruction, a pathological fracture, a bone deformity or a crushing of a vertebral body with a paraplegia is frequently the first sign of the bone lesion. Generalization of the disease through metastasizing to other organs is a feature of the natural life of a myeloma. However, frequently cases come to postmortem examination without metastases to soft organs. This is probably because the patients die early from the severe emaciation and intoxication as a result of extensive bone-marrow destruction.

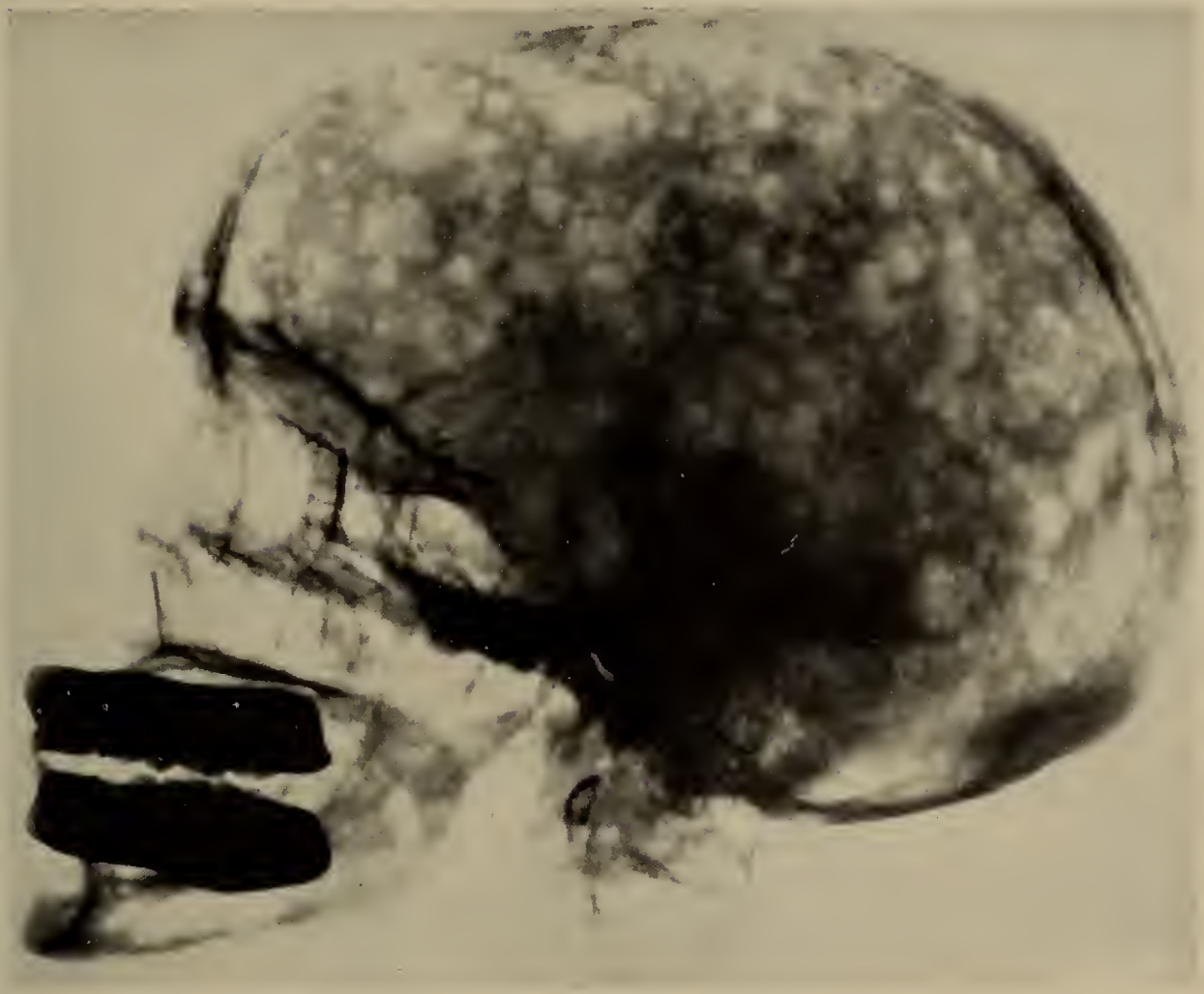


Fig. 73. Same case as shown in Figure 72. Myeloma in a woman 56 years old.

Secondary growths have been seen in the liver, spleen, kidneys, regional lymph nodes, and skin.

Diagnosis

The radiological method is the main one in the diagnosing of myeloma. The history and clinical picture of an early stage of the disease is not remarkable as far as diagnostic possibilities are concerned except in regard to multiplicity and situation. In a far advanced case the multiplicity of involvement suggests multiple myeloma rather than Ewing's sarcoma. The absence of pulmonary metastases in the presence of very extensive skeletal involvement is the rule in myeloma. The age of the patient is also suggestive of myeloma; they occur after 40 years of age. Albumosuria and the presence of Bence-Jones proteins in the urine which for a long time has been considered pathognomonic for myeloma, may be absent in a large percentage of cases—according to some observers in one half. On the other hand in occasional carcinomatous skeletal metastases and other medullary tumors the presence of Bence-Jones proteins has been observed.

For obvious reasons morphological blood studies, which, as a routine, should be made in all skeletal tumors, should never be omitted in myeloma. In the roentgenogram myeloma reveals well outlined, definitely circumscribed areas of diminished density. At one stage or other these areas may be large and single or small and multiple in the same bone spreading all along the medullary cavity. The bone is slightly expanded by the individual nodules so that the extremely thinned cortex is irregularly wavy in outline and not uniform in thickness (Figs. 72, 73). There may be minute nodules in the cortex itself. A perforation of the cortex is rare and so is an infiltration of the soft tissues about the involved bone. The very characteristic roentgenogram may be greatly obscured by frequent infractions or complete pathological fractures, which may present diagnostic difficulties. When myeloma is located in the spine it is difficult to identify the individual myelomatous nodules because of the greatly atrophied bone structure. Partial collapse of a vertebra and apparent disappearance of intervertebral discs is not an infrequent occurrence in myeloma of the spine. A radiological examination of the whole skeleton is extremely important.

In making a diagnosis from a histological section one has to keep in mind that an overstaining with hæmatoxylin may lead to mistaking Ewing's sarcoma for myeloma. Myeloma generally shows mild pleomorphism as compared to Ewing's sarcoma. An exploratory incision is both undesirable and unnecessary because of the promptness with which myeloma responds to radiation. The diagnosis is early established from the very characteristic roentgenogram.

Therapy and Prognosis

As a tumor composed of lymphoid cellular elements, myeloma is readily affected by radium and high voltage roentgen rays. The local growths disappear after repeated radiation, and pathological fractures may unite under such treatment, but ultimately death follows from extension and metastases. When the disease appears with multiple tumors there obviously can be no choice between surgical treatment and radiation, the latter being the sole recourse. In the rare instances of solitary myeloma, amputation may be justified and according to some observers it may for long postpone or even prevent metastases. However, the frequent location of myeloma in the spine and the sternum will decide against surgical treatment even in cases of solitary tumors. The histological variations of the tumor do not influence the effect from radiation. It is questionable, however, whether continuation of radiation is permissible when the leucopenia reaches 2,500. To prevent a pathological fracture, immobilization of the involved limb and recumbency is essential. On the whole myeloma may prove occasionally of decidedly better prognosis than other malignant bone tumors. Cases are on record in which ten and more years have passed between the clinical onset and the fatal termination of the disease.

UNCLASSIFIED SARCOMA

IN the group of "unclassified sarcoma" are included, aside from a few atypical instances, two conditions which are endowed with a typical anatomical structure and characteristic clinical behavior. The exceptional rarity of these conditions has prompted me to refrain from a segregation of them under separate headings in the classification. These tumors are angio-endothelioma and extraperiosteal sarcoma of bone.

ANGIO-ENDOTHELIOMA

Pathology

OUR knowledge of osteogenic sarcoma, Ewing's sarcoma, and giant cell tumor has gained tremendously from the Registry, but the latter has contributed little to the knowledge of angio-endothelioma. The pathology of angio-endothelioma of bone is still a very confused problem. The reasons are numerous. Since the days when Golgi, over fifty years ago, first offered the name "endothelioma" this term has been applied extensively to uncommon tumors both of soft tissues and of the skeleton. The at first sight histological resemblance of endothelioma to carcinoma has led to the diagnosis of endothelioma in cases of secondary carcinoma in which one failed to find the primary tumor. This error has been followed in our days by the tendency of pathologists to dodge the diagnosis of endothelioma and to substitute for it carcinoma even in cases in which much of the histological and clinical evidence is in favor of the former diagnosis. Further confusion was brought in by the fact that in the literature the rare primary angio-endothelioma of bone is confounded with an occasional secondary involvement of the bone by an endothelioma of the adjoining soft tissues. Such lesions are especially frequent in the skull where the endothelium lined dura represents the endosteum of the bones of the skull. The local changes in the skull overlying a dural endothelioma or meningioma, as Cushing calls this tumor, lead to the formation of a dome shaped bony prominence, which on section shows hyperostosis infiltrated by tumor elements from the underlying primary tumor of the dura. Often these changes in the skull have been mistaken for sarcoma, and in such cases the primary lesion, the tumor of the dura, was overlooked. It is easy to see how such an error can be made when it is realized

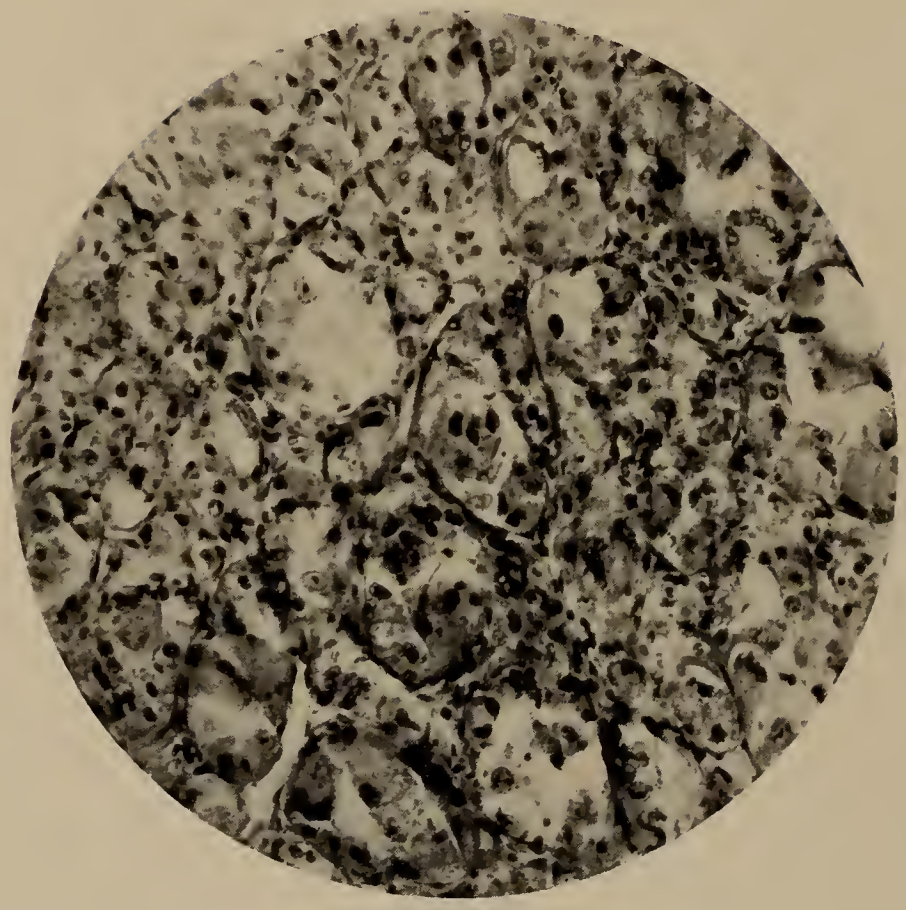


Fig. 74. Case 154. Same case as that in Figure 75. Skeletal angio-endothelioma. The tumor cells form alveoli and tubuli.

that the fan-like radiation structure of the hyperostosis in the roentgenogram is reminiscent of the structure frequently seen in osteogenic sarcoma. It is hardly necessary to point out here the dangers, on one hand, of mistaking a secondary tumor of the bone for a primary and, on the other hand, of confusing different types of tumor which have nothing in common clinically or anatomically. It is fully ascertained that endothelioma of the dura does not metastasize and is not even locally malignant as far as infiltration of the brain is concerned.

Another source of error arose in connection with the facts that microscopically one of the leading features of angio-endothelioma is the abundant vascularity; a confusion of angio-endothelioma with angioma and angiosarcoma is probably best explained by this fact. However this may be, this still further contributed to the confusion existing about angio-endothelioma of bone. Various interpretations by individual investigators of histological findings even in true angio-endothelioma of bone did not help much to clear this problem. Such a discrepancy of views and opinions is only natural when one realizes that the tumor is exceedingly rare, the men with most experience having seen only a few cases.

The knowledge of the embryological relations of the cells called endothelium is yet far from complete. However, it is fully attested that the endothelium is

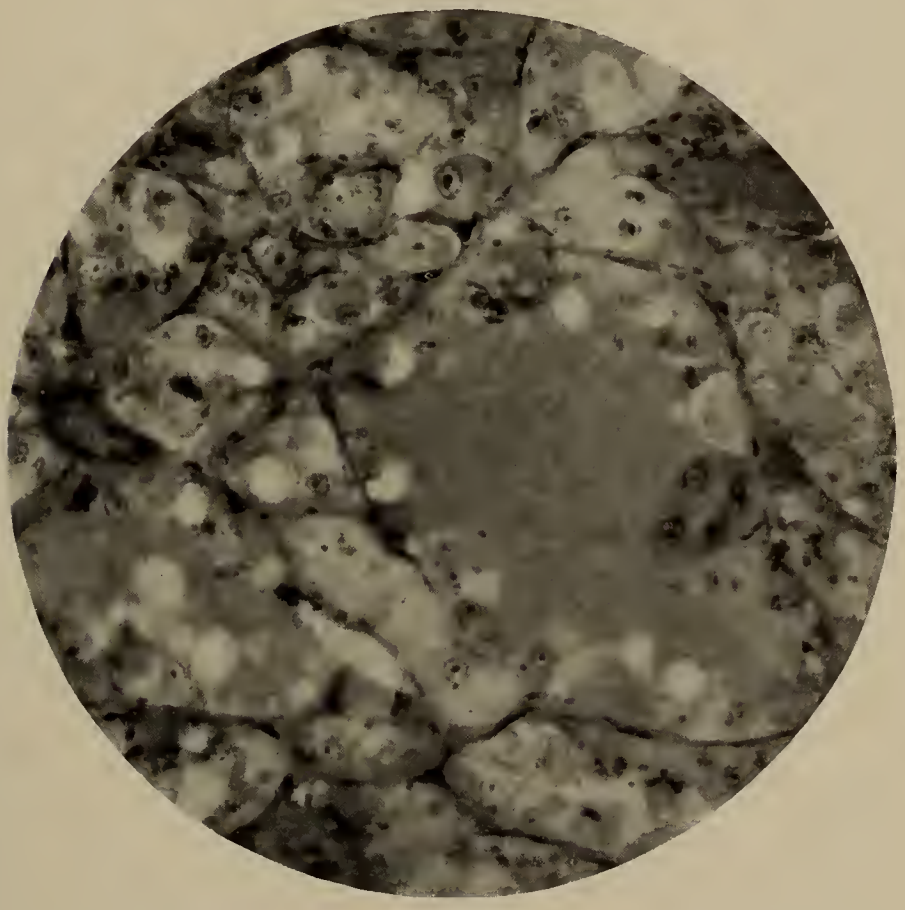


Fig. 75. Case 154. Same case as that in Figure 74. Skeletal angio-endothelioma. Alveoli with intact blood are lined by a single row of tumor cells simulating vascular endothelium.

derived from mesenchymal cells; it has differentiated along various lines because of its function—walling of vascular channels and spaces. As has been mentioned, angio-endothelioma of bone is a very rare tumor, the Registry having, in my opinion, only two cases. These two cases have been used by me in a special study with the intention of urging recognition of angio-endothelioma of bone as a definite anatomical entity.[1] It is obvious that no very extensive and definite conclusions as to their histology can and should be attempted,—it is not safe theoretically and it is of no importance from the clinical point of view. There is no sufficient evidence to support a distinction between hæm- and lymph-angio-endothelioma at least as far as bone is concerned; the numerous pitfalls surrounding such detailed studies in bone may lead to a confusion in which our meagre knowledge of angio-endothelioma of bone would be stripped of the facts at present fully attested.

In general features the most frequent histology of skeletal angio-endothelioma will at first glance impress one with the resemblance to an adenomatous growth.

[1]Kolodny, Anatole. A case of primary multiple endothelioma of bone. Arch. Surg., 1924, ix, 636. Idem. Angio-endothelioma of bone. Arch. Surg., 1926, xii, 854.

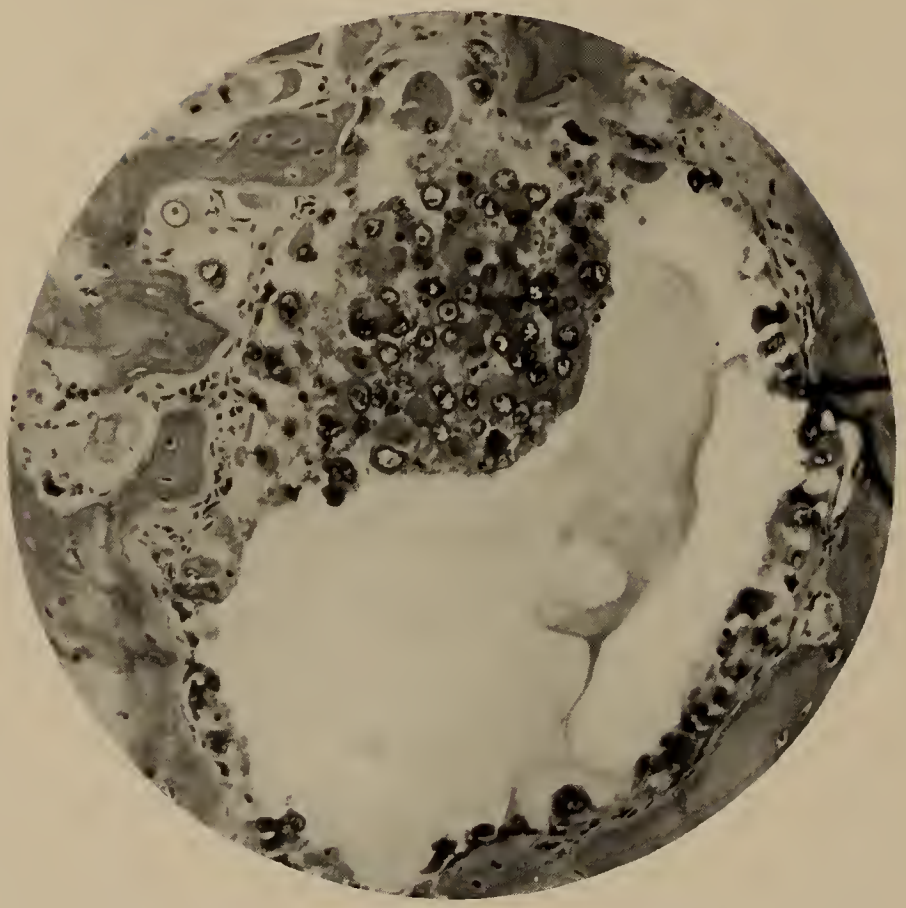


Fig. 76. Case 291. Skeletal angio-endothelioma. Showing proliferation and piling up of blood vessel endothelium.

The tumor cells are arranged in alveoli and tubules. The interalveolar septa form the base upon which the tumor cells are lined (Fig. 74). The cells may vary with the maturity of the tumor. In the young areas the alveoli are small, filled with tumor cells, without any perceptible lumina. The tumor cells are large polyhedral sometimes cylindrical with a well defined cell membrane and with pale vesicular nuclei and minute nucleoli. At a later stage the alveoli show lumina, sometimes filled with circulating blood. At a still later stage the tumor cells are undergoing degenerative changes. The most interesting feature is the frequent lining of alveoli with intact blood by a single row of tumor cells well simulating vascular endothelium (Fig. 75). It is not uncommon to be able to trace the origin of the tumor cells to normal appearing blood vessel endothelium (Fig. 76). In some cases the tumor cells do not enclose intact blood but form small alveoli or small cysts containing mucinous material. The cells may be more cylindrical and quite resemble carcinoma. A common feature is the fact that the strands of tumor are intimately connected with the supporting stroma and the surrounding tissue and are not separated from it by means of endothelial cells lining the connective tissue spaces, as is always seen in carcinomatous metastases. Well differentiated and low grade new formed bone may be seen

throughout the tumor. The question of the relation of the supporting stroma to the tumor elements is disputable; there is strong evidence on hand, however, that endothelioma may give rise to intercellular substance and fibrils as was described by Lubarsch and Marchand with reference to serous endothelioma.

There is described in the literature another type of endothelioma, a so-called intravascular variety which to my knowledge is not represented in the Registry material at all. This variety, usually multiple, consists of diffuse cords and sheets of clear polyhedral cells often surrounding capillaries with circulating blood. The possibility of the relationship of these tumors to myeloma is inadequately recognized, and the possibility is greater since these tumors have a myelogenous origin and not an endothelial one.

Clinical Course

Clinically angio-endothelioma of bone so much resembles osteogenic sarcoma that it is commonly submerged under the diagnosis of "bone sarcoma." The tumor is too rare a condition to allow definite conclusions as to the clinical incidence, age, and site of predilection. The fact that only two cases were recognized by me in the Registry material suggests that the clinical incidence is extremely low. The tumors may be encountered in old as well as in young. They seem to be prone to occur in any bone of the skeleton, especially in the long bones. Subjectively the clinical symptoms and signs are in general the same as those in osteogenic sarcoma, save perhaps for a later date of appearance of pain. The tumors may grow to a large size. In one of the cases (No. 154) the tumor led to absorption and destruction of bone while in the other (No. 291) a definite inclination to bone production was evident. In the first case no bone capsule was present and the periosteum was found free of any osseous tissue while in the second bulky osteoblastic tumors were produced. It is thought that angio-endotheliomata have a tendency to remain long enclosed in their investing capsule. Apparently the tumors may be single and multiple, while it is impossible to determine whether or not the multiple tumors are metastases of one primary tumor. The tumors may produce metastases through the blood and lymph stream, ending fatally from pulmonary metastases. While the clinical course is slightly slower than that of an average osteogenic sarcoma, the outcome is the same.

Diagnosis

The rarity of angio-endothelioma of bone and the scarcity of material available for study make obvious the peculiar diagnostic difficulties of this tumor. Unlike other malignant bone tumors the history and clinical appearance of angio-endothelioma is of no diagnostic significance. For the same reasons little can be expected from the radiological examination. Indeed, there are no points of diagnostic value because of the diversity of features of this tumor, the tumor

occurs in young and old, solitary and multiple, destructure—with apparent complete washing out of the bone shadow in the roentgenogram—and productive—with formation of large bulky bony growths. The diagnosis rests upon the histological structure of the tumor. But here also numerous pitfalls make a correct diagnosis difficult. The salient features of the histological structure of angio-endothelioma have been pointed out above. There are, however, certain points which are of especial importance in diagnosing the tumor. One of the main features which cannot be overemphasized is the fact that the presence of blood between acinous clusters of tumor cells is not to be considered as evidence that the cells formed a vascular space during the life of the tumor. Neither does the so-called perithelial arrangement of tumor cells mean that the tumor is an angio-endothelioma. The lack of realization of this fact has led to the erroneous diagnosis of these tumors as angio-endothelioma in numerous instances.

Another important and frequent source of error arises from too large expectations of a study of morphology of the tumor cell. There are no absolute signs of an endothelial cell, and one can never be certain from the morphological appearance that a given cell is really endothelial. From this fact, one infers that unless the origin of the tumor cells can be traced to vascular endothelium, the diagnosis of angio-endothelioma is not to be considered unquestionable.

In every case of suspected angio-endothelioma the possibility of a metastatic origin must be considered and eliminated. It is imperative to remember that a hasty pathological examination may lead to an erroneous diagnosis. In the literature cases of angioma and endothelioma of soft parts with secondary involvement of the adjoining bone were often confounded with angio-endothelioma.

Since angio-endothelioma does not respond in a noticeable degree to radiation, a therapeutic radiation test is probably of no promise. An exploratory incision is of doubtful advisability in these tumors; while such incisions are subject to all hazards of cutting into a malignant tumor the diagnostic advantages of exploration promise little here since no method is known to influence the course of the tumor or to prevent metastases after radical surgery.

Therapy and Prognosis

The question of the therapy in angio-endothelioma as it stands today is wide open. We have not the slightest conception about influencing the growth and fatal course of this tumor. The few cases observed do not allow any valuable conclusions as to the therapy. The limited experience gained, however, does show that there are no surgical cures and no improvement from radiation, roentgen ray, or radium; this despite the vascular structure of the tumor. Early metastases and multiple origin of these tumors still more aggravate the prognosis of this disease. Purely symptomatic relief is the only help that can be offered patients afflicted with this disease.

EXTRAPERIOSTEAL SARCOMA

Pathology

As was pointed out in the chapter on classification, by the term extraperiosteal sarcoma is understood a tumor which is intimately related to the periosteum but is entirely extracortical, not invading or infiltrating the bone. This tumor arises from the fibrous layer of the periosteum and not from the bone producing cambial layer. Thus, this tumor arises from nonspecific fibrous tissue which is incapable of producing osseous tissue. This difference between this tumor and osteogenic sarcoma substantiates the pathology, gross and microscopic, the radiological features, and the clinical course. Since this tumor originates from or is attached to the fibrous layer of the periosteum its investing capsule is not formed by the periosteum as is the case in osteogenic sarcoma. These tumors remain encapsulated for a long time and in their growth they push aside the soft tissues rarely infiltrating them.

While as a rule these tumors do not invade the bone, they may, however, cause absorption or slight erosion of the bone as a result of pressure, or they may push aside the adjacent bone and cause deformities. In cut section the tumor is firm, fibrous, white, glistening, with easily distinguishable fasciculi; occasionally it is cellular, soft, and crumbly, when regressive changes are extensive. In such tumors we see necrotic areas with formation of cysts filled with a dark brown fluid, probably a result of necrosis with extravasation. Histologically these tumors do not show any relationship to bone and this relationship is to be judged from the gross anatomy. The leading histological picture of this tumor is that of a fibrosarcoma. Its various sized cellular elements are of the spindle cell type. These cells resemble fusiform fibroblasts and when loosely arranged their granular cytoplasm can be easily seen. When compactly grouped, these cells show no cell borders, the nuclei seemingly occupying the whole field. Elongated processes of the cytoplasm form a distinct intercellular substance consisting of abundant fibrils. With the increase in size, the tumor cells may be pleomorphic. By special methods of staining one can readily bring out a fibrillar intercellular substance loosely arranged between borders of spindle cells. In rapidly growing tumors one sees abundant capillaries consisting of single rows of endothelial cells; on a superficial examination it appears that blood courses in lumina composed by tumor cells without any help of endothelial cells.

Clinical Course

The very few reported cases in the literature and the very limited number of tumors resembling extraperiosteal sarcoma on record in the Registry seem to indicate that the clinical incidence of this disease is very low. The difficulty of distinguishing with certainty these tumors histologically from fascial sarcoma and the ease with which the relationship of these tumors to the periosteum may remain unrecognized at operation probably cause a misrepresentation of the clinical incidence. In their onset, course, and physical findings these tumors hardly differ from fascial sarcoma. The relationship of the tumor to the bone, a broad attachment to the periosteum, may not be judged from the pre-operative findings on palpation; large tumors may be freely movable despite their attachment to the periosteum of the bone. There does not seem to be any definite relationship between the incidence of the tumor and age; I have observed one case of extraperiosteal sarcoma of the tibia in a newborn child, at present alive and well, 10 years after amputation of the thigh.

Diagnosis

With the difficulty of distinguishing an extraperiosteal sarcoma from a fascial sarcoma even at operation it is evident that the pre-operative diagnosis must be largely provisional. The roentgenogram, however, may give some points suggesting the diagnosis. Usually the roentgenogram shows an intact or slightly eroded shaft of the bone running through a tumor mass which is poorly outlined because of the faint shadow that it casts. The tumor does not surround the bone circularly. Since the periosteum does not actively react to the presence of the tumor one does not see here the periosteal spindle or lipping so frequently manifested in osteogenic sarcoma. Since the tumor does not invade the bone but may cause pressure deformity one may encounter roentgenologically changes in the contour of the bone. Occasionally the tumor may lead to proliferative processes of the bone to which it is attached; the outline of the bone then remains smooth as in benign osteogenic tumors. Sometimes the tumor causes superficial erosion of the bone. In such tumors of fingers or toes one is reminded of gout when the bone is eroded, but instead of being rarefied, atrophic, it is denser than normal. A gout tuft can be easily recognized grossly from the gritting of the uric acid crystals when cut with a knife (Plate 8).

Therapy and Prognosis

Radical surgical removal is the operation of choice in extraperiosteal sarcoma. Thorough incision may be followed by permanent recovery. A considerable number of cases reported in the literature as cures of "bone sarcoma" after surgical operations probably belong to the extraperiosteal sarcomata. The

prognosis is especially favorable when the tumor is found encapsulated. After incomplete excision these tumors may recur but with a moderate tendency to produce metastases. Recurrence is not unusual in the large, more actively growing tumors in which regressive changes are frequent. With the recurrence, the texture of the tumor may become more anaplastic and malignant. Not uncommonly the intimate relationship of the tumor to the periosteum is overlooked at operation, the extraperiosteal sarcoma is mistaken for a fascial sarcoma and the attachment to the periosteum is left behind. Surgical removal of a fibrous sarcoma located close to a bone therefore should be followed by prophylactic radiation therapy, preferably with roentgen rays.

GIANT CELL TUMOR

Pathological Concept and Etiology

THE clinical and pathological aspects of giant cell tumor of the skeleton are so at variance with the malignant skeletal tumors that a discussion of the disease here calls for explanation. As is inferred by the name, by giant cell sarcomata are understood lesions the histological structure of which is characterized by an abundance of giant cells. However, such a definition of giant cell sarcomata would be erroneous since not all tumors showing the presence of giant cells belong here. Three types of giant cells can be distinguished in pathological conditions. First come the giant cells which are a result of karyorrhexis in the cellular elements of the tumor. This is especially frequently observed in rapidly growing malignant tumors where the division of the cytoplasm cannot keep pace with the closely following, repeated divisions of the nucleus. The nuclei here are of various sizes and shapes, frequently not completely separated from each other. These giant cells are a significant part of the parenchyma of the tumor. Following the lead of Mallory these are spoken of as true tumor giant cells. Another type is the so-called foreign body giant cell. These occur in tuberculosis and in gummata; they are the Langhans type of giant cells with a peripheric or bipolar arrangement of their nuclei. The third type is represented by the giant cells of the so-called giant cell sarcoma which is here designated as giant cell tumor. The nuclei are uniformly distributed throughout the central portion of the cell; they are of equal size and completely separated from one another. The fact is still insufficiently realized that only lesions with giant cells of the third type are understood under the term of giant cell tumors. Skeletal lesions designated as giant cell sarcomata are of three varieties: (a) the giant cells containing new growths observed in the course of osteitis fibrosa, (b) the epulis, and (c) the giant cell tumor. The lesions marked under (a) are generally conceded to be of purely inflammatory character and obviously do not belong in the present analysis. Epulis, as the term infers, is a lesion of the gums or alveolar periodontium rather than of the bone itself. The benign course of epulis has been generally realized for a long time and to include epulis in our present study of giant cell tumors could be justified merely for reasons of emphasis, for such an association would tend to stress the point of benignity of giant cell tumors.

The term giant cell tumor is applied to a condition which has been and still is known in various countries and even in one and the same country by different

names. *Tumeur à myéloplaxes* given by Nélaton has changed to myeloid sarcoma and myeloma, which is still being used in the British literature; it is also known as giant cell sarcoma, benign giant cell sarcoma of the epulis type, giant cell sarcoid, osteitis fibrosa cystica, hæmorrhagic osteomyelitis, and giant cell tumor. The benign character of giant cell tumors is not yet generally recognized, and not infrequently the lesion is still looked on as a sarcoma. The fact that hundreds of cases of giant cell tumor have been sent to the Registry of Bone Sarcoma by clinicians and pathologists the country over is sufficient justification of the necessity of the discussion of this lesion in a monograph primarily dedicated to malignant bone tumors.

The question of the etiology of giant cell tumors is at first glance intricately interwoven with an academic question: Is giant cell tumor a neoplasm or a product of inflammation and repair? The acceptance of the name giant cell tumor as a substitute for all other names of this lesion is not to be looked upon as proof of the neoplastic nature of the lesion; the term "tumor" is used here merely in a clinical sense, that is, to indicate a swelling, inasmuch as the pathological anatomical sense of this word is at present not entirely clarified. The question of whether a giant cell tumor is a true blastoma or merely an inflammatory process follows an old trodden path of discussion; a similar question was in vogue twenty-five years ago in relation to the new growths observed in the course of osteitis fibrosa. It was Mikulicz who then in the light of contemporary knowledge warned against the wrong assumption that bone cysts are results of true tumors which have undergone softening and degeneration. As it stands today the concept of the disease known as giant cell tumor divides investigators in two opposing classes. To one belong those who look upon a giant cell tumor as a true blastoma and to the other those who see in it merely a product of inflammation and repair in bone. Since the view upon giant cell tumor as a true blastoma is supported by tradition, the burden of proof in this dispute lies on the promulgators of the inflammatory nature of giant cell tumors. The leaders among these are Mallory, Codman, and Barrie in this country and Lubarsch and Konjetzny in Europe. Mallory has long maintained that the giant cells of the giant cell tumor are not an integral part of the lesion but only a biological reaction of the large mononuclears of the blood, the so-called endothelial leucocytes, which are found wherever retrograde changes are going on. As a reaction to calcium salts absorption these endothelial leucocytes fuse and form the giant cells. Aside from these giant cells no cells occur in these lesions which are not met with in ordinary inflammatory processes. Of the same opinion is Codman who sees in the giant cell tumor a repair process following intra-osseous hæmorrhages due to rupture of nutrient vessels. In Codman's opinion the tendency of this disease to form large expansive tumors does not warrant considering it as a neoplasm any more than does the enlargement of an aneurysm.

Strongly substantiated by results of special investigations are the opinions of Lubarsch and Konjetzny. Years ago Lubarsch had pointed out with the clarity and logic usual for him that the new-growths observed in the course of osteitis fibrosa are of purely inflammatory nature. Later he joined Konjetzny in the latter's interpretation of results obtained from special studies of giant cell tumors. On the side of histological preparations Konjetzny showed how an intermedullary hæmorrhage calls forth a reactive proliferative process. The product of this proliferative process of the bone-marrow which can be compared to granulation tissue consists histologically of all the elements encountered in lesions known as giant cell tumor. The clinical course and the radiological findings are very closely related to those of giant cell tumors. In the course of the natural life of this granulation tissue there is a stage of differentiation when fibrous tissue, osteoid, and sometimes osseous tissue take the place of the hæmorrhage after it has subsided, the blood clot organized, and all the foreign elements removed. Thus Konjetzny concludes that the apparent tumor is merely a "chronic-resorptive process."

The opponents of the opinion that giant cell tumors are true blastomata emphasize the following points of the histology of giant cell tumors as supporting their views: the absence of pleomorphism of the cellular elements and of hyperchromatism of the nuclei and the absence of excess of mitoses; the differentiation of the cellular stroma into dense fibrous tissue poor in cells; the uniformity in the size, shape, and chromatin content of the giant cell nuclei; the relation of the giant cells to extravasations, indicating their rôle in resorption; and the constant presence of old blood pigment. All these features are not inconsistent with the probable inflammatory nature of these lesions. If one admits the correctness of the views of these authors with reference to certain skeletal lesions and especially to the new growths occasionally observed in the course of osteitis fibrosa one is, however, prompted to accept the contention that along with these lesions there probably are also true blastomata very similar to these clinically and histologically. It is generally conceded how difficult it is to distinguish histologically between a new-growth in osteitis fibrosa and entirely independent lesions considered as giant cell tumors. Of course this fact alone is sufficient evidence to raise doubt as to the right by which giant cell tumor is occupying its place in oncology. On the other hand there is no sufficient evidence accumulated to support the contention that in all cases of giant cell tumor the lesion is a process of inflammation and repair.

The etiology of the typical giant cell tumor is readily understood if one accepts the new-growths observed in the course of osteitis fibrosa cystica as giant cell tumors. The term "osteitis fibrosa" is being greatly misused of late. The average roentgenologist is usually inclined to call osteitis fibrosa most of the bone lesions which he is unable to diagnose and classify. This fact well illus-

trates the need of further study of this little understood pathological condition. The main complex of osteitis fibrosa is the disappearance of hæmatoblasts and fat cells from the bone-marrow with a subsequent overgrowth of the fibrous stroma and lymphoid elements. This is accompanied by a simultaneous resorption of bone and new formation of osteoid tissue, and this leads later in the course of years to fractures and deformities. Frequently, in the course of the disease one encounters formation of cysts. Hæmorrhage into the cysts may lead to an overgrowth of masses, resembling granulation tissue, which may enlarge and finally be recognized as giant cell tumors. The purely inflammatory nature of these lesions has been emphasized above. The frequent history of an antecedent mild trauma in giant cell tumor has led to the recognition of trauma as an important etiological factor. As in malignant bone tumors, much depends upon the individual concept of trauma. It has been shown that a hæmorrhage into the bone-marrow may lead to cyst formation as it is observed in the brain. Organization of the intramedullary hæmatoma with the appearance of the peculiar medullary granulation tissue and expansion of the bone will then form the giant cell tumor. Very slight traumatization is frequently sufficient for the appearance of medullary hæmatomata. While it is usually thought that fractures are not the cause but merely a complication of giant cell tumor and osteitis fibrosa, it is probable that fissure fractures or, better, infractions with the rupture of nutrient vessels may lead to the formation of a giant cell tumor. The frequent presence of old hæmorrhage histologically in a giant cell tumor and the almost exclusive location of giant cell tumor in the ends of the bone in the spongiosa seem to support this view. Wright and Ewing brought forth evidence of the origin of variants of giant cell tumor from absorption of aberrant islands of cartilage cells which are not unusual in patients suffering from rickets in childhood. This absorption may lead to a neoplastic proliferation of the released cells. All mentioned factors, however, fall short of a satisfactory explanation of the etiology of all varieties of giant cell tumors and cases are encountered in which the etiological factors remain obscure for the present.

Pathology—*Gross Anatomy*

As in osteogenic sarcomata, the gross anatomy of giant cell tumors depends largely upon the destructive and productive processes of the involved bone. The tumor tissue during its period of growth constantly destroys the bone while the periosteum lays down an advancing shell of new bone, thus preventing the tumor mass from an early perforation of the bone and an involvement of the adjoining structures. It is due to a combination of these two opposing reactions of the involved bone that the giant cell tumor is an expansible but not infiltrative or invasive lesion encapsulated in a bone shell. Eating its way into the bone, the tumor tissue destroys the bone from within the medullary cavity, gradually

Fig. 77. Courtesy of Warren Museum, Boston. A macerated specimen showing the skeleton of a giant cell tumor. It shows the sharp limitation and general expansile character of the tumor. Notice the extension over the top of the fibula without involvement of the latter. In some cases the tumor enters the fibula by way of spreading the ligamentous attachments between the bones (Plate 35). A partial pathological fracture is seen.

expanding the old cortex, while a few more or less thick bony trabeculæ running in various directions line the cystically expanded bone shell simulating beams supporting the whole structure. It is this structure that causes the most characteristic "soap bubble" appearance in the roentgenogram. The structure of a skeleton of a giant cell tumor is best studied in the macerated and dried specimen when the soft spongy tissue is removed (Fig. 77). Thus the investing capsule of the giant cell tumor is furnished by the new formed bone shell and the periosteum. The latter, while distinctly thicker and more vascular than on the adjoining uninvolved cortex, does not form, however, the abrupt elevation, the periosteal lipping, which is so typical of osteogenic sarcoma. When nothing interferes with the advancing growth of the tumor, the bone shell may be gradually thinned and finally entirely disappear in places. Long after the bone shell is thus perforated the periosteum still continues to envelop the tumor until a very advanced development of the tumor or a pathological fracture hastens the perforation of the periosteal capsule. This is in marked contrast to a malignant bone tumor where the perforation of the bone and periosteum occurs very early. Another factor leading to perforation of the periosteum in giant cell tumor is an exploratory incision although followed by suture of the periosteum. On a longitudinal section through a giant cell tumor

Fig. 78. Case 454. Same case as that in Figure 84. Giant cell tumor in a man 28 years old. The arrow points to the limiting membrane of the lesion, toward the medullary cavity.

one occasionally recognizes grossly a limiting membrane toward the medullary cavity; a thin layer of brown whitish tissue beyond which the normal spongiosa or bone-marrow can be seen (Fig. 78).

The articular cartilage is very resistant in giant cell tumor as it is in osteogenic sarcoma. It is most unusual to see the articular cartilage destroyed by tumor tissue even in the advanced stage. Usually the spongiosa lining the articular cartilage from within the medullary cavity is entirely destroyed and the cartilage is in immediate contact with the tumor tissue (Plate 34). In such a proximity of the tumor to the joint cavity one may find the synovial membrane slightly thickened, œdematous, of brownish yellow color. It is not unusual to find some clear exudate in the joint cavity. An actual direct involvement of the joint cavity by tumor tissue is even less frequent than in osteogenic sarcoma; it occurs in pathological fractures and in very advanced cases. It is not unusual, however, to see an indirect involvement of the joint cavity by tumor spreading along intra-articular ligaments, for instance along the ligamentum teres femoris or ligamenta cruciata. The same manner of growth of the tumor, by spreading the lamellæ of ligaments, one sees also in involvement of an adjoining bone when the ligamentous attachments between the bones usually serve as a bridge for the

Plate 34. Case 580. Giant cell tumor. The roentgenogram was taken before amputation. The extent of involvement in giant cell tumor is always greater than it appears from the roentgenogram. The apparent limitation of the tumor to the external condyle is misleading as is seen from the photographs. Above, right, section through the external condyle; it shows the intact articular cartilage, while the entire condyle is displaced by the lesion. Below, right, section through the internal condyle.

tumor (Plate 35). This way of expansion of the tumor along lines of lesser resistance is also observed in the process of perforation of the periosteal investing capsule where the layers of the periosteum are spread by the ingrowing tumor tissue; it is also seen in the spreading along fascial planes of the tumor mass projecting into the soft tissue after periosteal perforation. In far advanced and large giant cell tumors the expansion of the bone shell is interfered with by the surrounding tendons and ligaments, so that occasionally the röentgenogram, but more frequently the dried specimen, shows grooves in the bone shell through which the individual tendons ran (Fig. 79).

The gross appearance of the giant cell tumor depends greatly upon the phase of the lesion. The typical giant cell tumor consists of solid portions and numerous small cysts. The solid portions are very friable, crumbly, somewhat granular masses, varying in color from yellow and light brown to dark red. On incision the tumor tends to extrude like granulation tissue. The texture of the growth becomes more dense with the approximation to the periphery and capsule. This vascular, soft, readily oozing, and frequently profusely bleeding tumor, resembling currant jelly, is entirely confined within the bone shell; it lies there loosely and can be easily scooped out by a curette. With the aging of the tumor or after radiation therapy the tumor mass enters a cicatrizing phase. The reddish jelly-like tumor mass changes gradually, beginning at the periphery, to a more opaque and firm mass, while in the central portion the old juicy stroma prevails. With the advancing differentiation of the tumor tissue, fibrosis in all stages to fibrosis and cicatricial tissue may be seen. Some varieties of giant cell tumors may be solid and firm throughout from the commencement and because of their frequent peculiar yellow color due to the presence of lipoid material they have been designated as xanthomata. The variety of giant cell tumors which, according to Wright and Ewing originates from absorbing of aberrant cartilaginous islands, shows the presence of various sized foci of cartilage distributed in the giant cell tumor mass. The various phases of giant cell tumor are a result of advanced differentiation of the soft immature tumor tissue. All successive processes of repair can be traced here. Such a differentiation is especially marked in well advanced cases. A pathological fracture through the tumor or radiation therapy, as well as an incomplete surgical curettage, may give rise to a cicatrization of the tumor. When a giant cell tumor is complicated by a fracture the soft hæmorrhagic giant cell tumor tissue is replaced by active fibrosis which is followed by peripheral ossification. Usually, however, the outer part of the tumor alone is fibrosed, the central portion remaining in its immature stage or being replaced by a fluid containing cyst. The firm, dry, fibrosed peripheral portion may show osteoid tissue formation and even ossification.

At the suggestion of Ewing an attempt has been made to differentiate several varieties of giant cell tumors which differ from the typical tumor grossly as well

Plate 35. Case 212. Giant cell tumor in a man 24 years old. Curettage on several occasions led to a persistent sinus with tumor sprouting through it. The roentgenogram was taken before the amputation, 2 years and 2 months after the onset. The roentgenogram and especially the photograph show the spreading of the tumor along the tibia—fibular attachment into the fibula.

as histologically. Thus, as xanthoma is designated a variant of giant cell tumor in which the presence of considerable fatty detritus lends the tumor a yellow appearance. Another variant is the so-called myxomatous giant cell tumor in which a mucinous matrix is the main characteristic feature. Giant cell tumors in whose texture islands of cartilage are encountered are said to arise from absorption of misplaced islands of cartilage, when the released cartilage cells acquire a neoplastic character. In this variety of giant cell tumor it is not unusual to see extensive areas of calcification about the remnants of cartilage cells. As in osteogenic sarcoma here also the degree of vascularity of the tumor has been laid as a basis of differentiation of a so-called telangiectatic giant cell tumor. Already in a typical giant cell tumor the central portion is made up either of an organizing blood clot or a sinusoidal reticulo-endothelial system filled with grossly intact blood, reminding one of a bloody sponge. When the extensive vascularity is confined not merely to the center of the tumor but is present in the largest portion of the tumor, it then represents the telangiectatic variety of giant cell tumor

(Plate 36). The clinical importance of such a differentiation of variants of giant cell tumor is questionable since there is no sufficient evidence accumulated to support the contention that these variants differ greatly in their clinical course. Furthermore, such variants cannot be distinguished before the tumor is submitted for a pathological examination, gross or histological.

Fig. 79. Courtesy of Warren Museum, Boston. A dried specimen of a giant cell tumor of the lower end of the radius. Showing the grooves for the tendons and the ballooning of the styloid process. The nodule at the top of the styloid process apparently belongs to the carpal bones. The patient, a woman, died in 1850 from a natural cause.

The rich vascularity of giant cell tumor alone suggests the great tendency of the tumor tissue to retrograde change; the frequent presence of blood clots, of old blood pigment, and of areas of hæmorrhage in all stages of decomposition is sufficient evidence of the frequency with which regressive changes occur here. After radiation therapy of a giant cell tumor it is not unusual to see in the central portion extensive necrosis and cyst formation filled with blood clot and serous fluid. The occurrence of cysts in an advanced giant cell tumor is not uncommon. Occasionally the polycystic appearance is very striking. Various cysts, reaching the size of a hazel nut, are confined within chambers formed by brownish septa, at times paper thin and then again of considerable thickness, interwoven among themselves and at the periphery rather firmly attached to the bone trabeculæ of the bone shell. The cysts are filled with blood or chocolate colored fluid (Fig. 80); or an opaque, brownish, or greenish mucinous mass, a greenish or grayish serum; evidently the product of various stages of decomposition of blood extravasations.

Structure

The histological structure of the typical giant cell tumor consists of two leading elements: the giant cells and the stroma. The latter consists of numerous

Fig. 80. Case 320. Same case as that in Plate 36. Giant cell tumor of the tibia in a woman 35 years old. Amputation 3 years after the onset. Showing complete absence of a periosteal reaction on the adjoining portion of the uninvolved shaft.

various sized blood spaces and exceedingly thin walled capillaries suspended in a very loosely woven net of spindle, round, or polygonal cells with large vesicular nuclei. One of the most characteristic features of a giant cell tumor is the absence of pleomorphism of the cells of the stroma. This loose cellular tumor mass is very poor in fibrils in contrast with the peripheral portion of the tumor where the differentiation of the cellular elements usually begins first, and where the stroma is poorer in cells but firmer through the abundance of fibrils. In the central portion of the tumor fresh extravasations of blood as well as hæmosiderin can be found; the latter, however, is usually found near the periphery of the bone shell. With the advancing growth of the tumor the blood clot may organize, and the blood pigment is carried away by giant cells and by the abundant endothelial leucocytes sprinkled through the tumor mass. It is in these endothelial leucocytes and not in the cells of the stroma that mitoses are not infrequently observed.

The numerous giant cells are loosely embedded in the stroma (Fig. 81). These are large opaque acidophile cells, resembling normal osteoclasts and containing numerous small oval nuclei uniformly shaped with a chromatin content larger than the nuclei of the stroma cells. The nuclei are grouped in the central portion of the large cells. The histogenesis of this peculiar cell is still a subject of discussion; the theory in vogue at present is that these cells originate from the endothe-

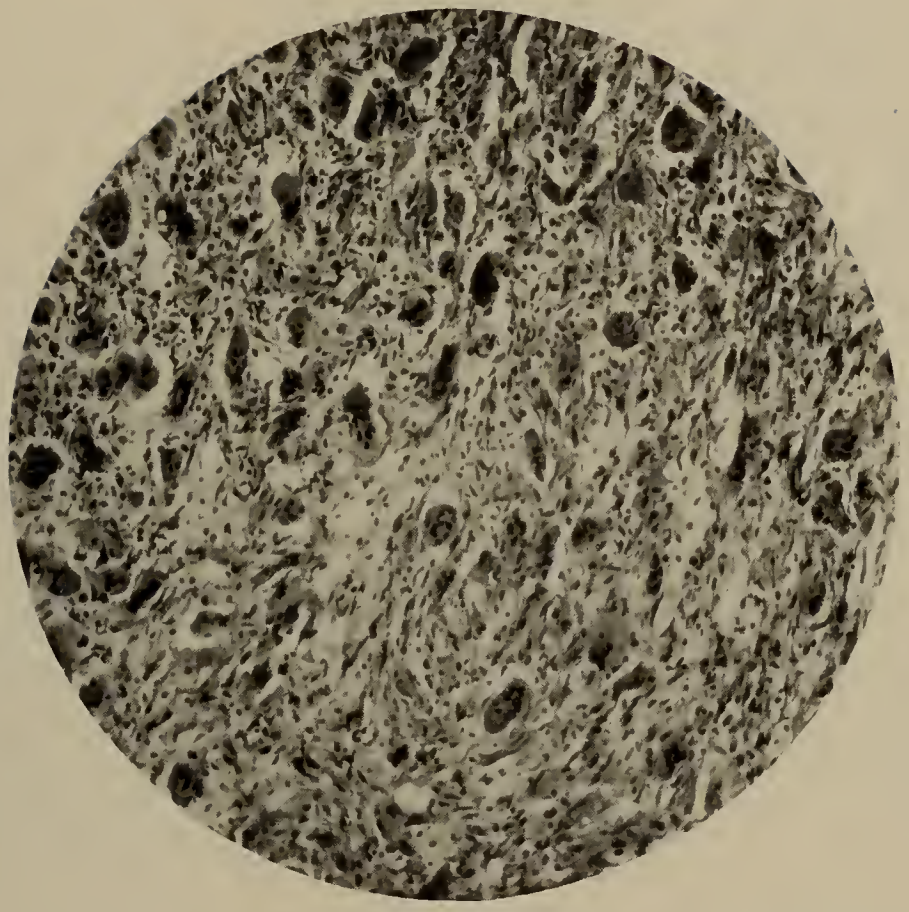


Fig. 81. Case 208. A typical structure of a giant cell tumor. Abundant giant cells of epulis type are loosely embedded in a fibroblastic stroma.

lium. The very intimate relation of the giant cells to the vascular endothelium, the frequent lining of blood spaces by giant cells, and the tracing of the formation of giant cells to the proliferative vascular endothelium seem to support Lubarsch's view of the giant cells as abortive vascular sprouts. Mallory believes the giant cell to be a product of fusion of endothelial leucocytes in the presence of calcium salts absorption. In a study of the giant cells as they are seen in various stages of giant cell tumors one can trace their composition from smaller cells as well as their splitting up in cells with single nuclei. Apparently after the need for the giant cell has passed they have a tendency to disunite. Frequently, however, one sees the retrograde changes leading to the terminal end—death of the giant cell. Minute clefts and small vacuoli appear in the cytoplasm; the latter are probably traces of fatty detritus which was phagocytized by the giant cell and removed from the cell in the course of the histological preparation. If the cytoplasm has not disappeared in the process of splitting up of the individual nuclei, it may remain as a dead, faintly stained clump of cytoplasm riddled with vacuoli and shadows of the nuclei. Such cytoplasm may break up in small débris and be finally removed from the tumor by other phagocytes (Plate 37, frontispiece).

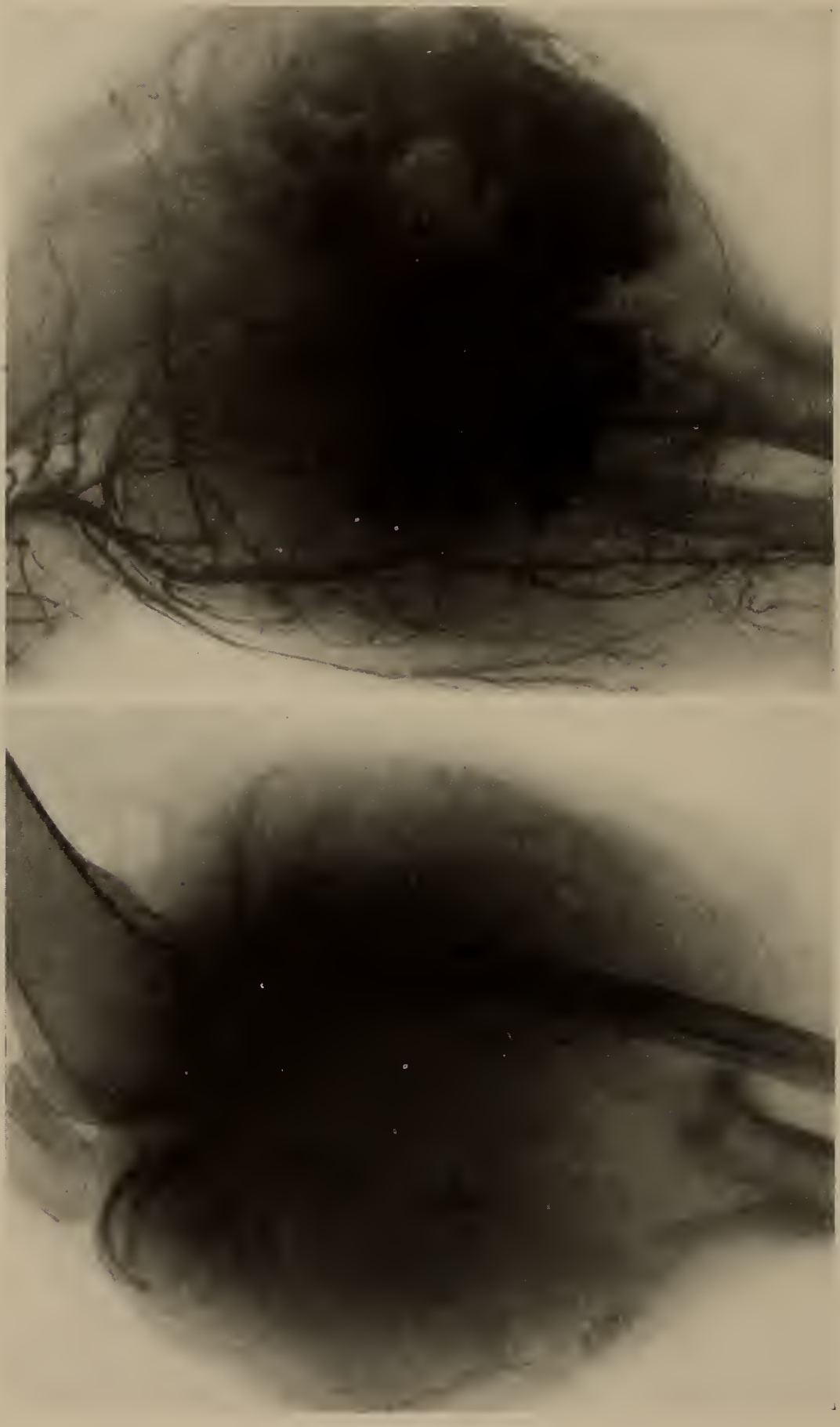


Plate 36. Case 320. Same case as that in Figure 80. Giant cell tumor in a woman 35 years old. Radiation was attempted but unsuccessfully, apparently because of the immense size of the tumor. Amputation 3 years after the onset. Showing the huge blood spaces in relation to the main blood vessels.

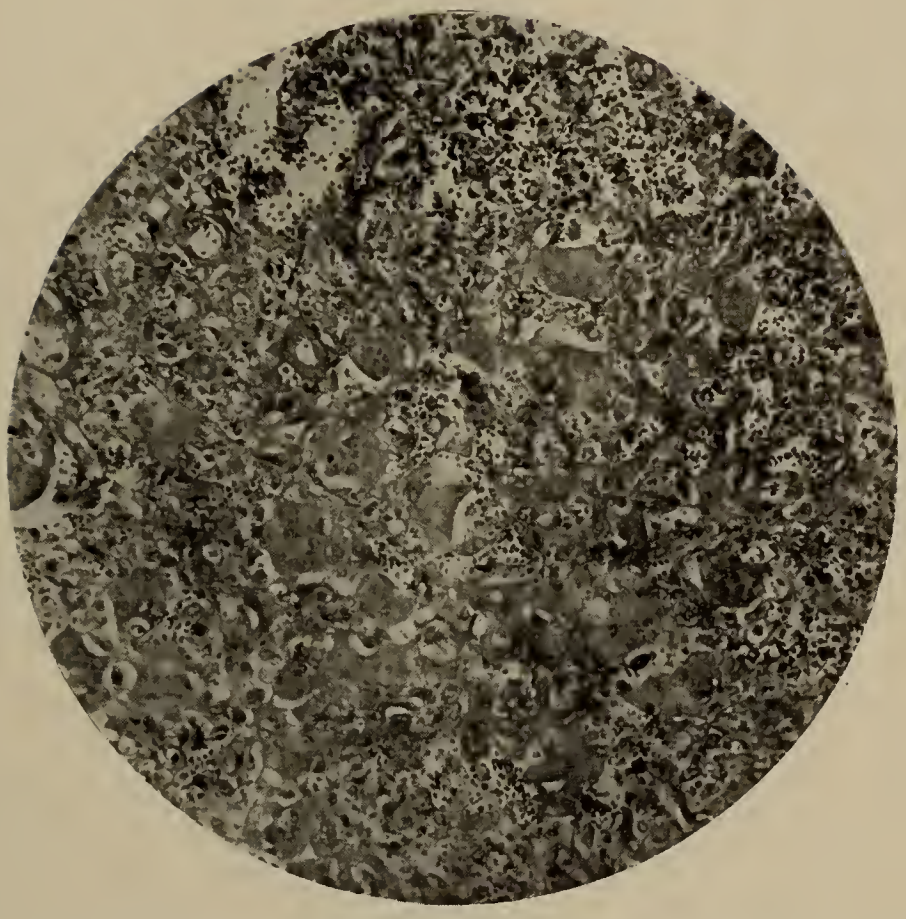


Fig. 82. Case 142. Giant cell tumor. Showing the net-like structure of the spongy tumor with the giant cells playing an active rôle in the texture of the tumor.

There is at present much discussion whether the giant cell is an integral part of the tumor or merely a side product called forth for the scavenger work in the lesion loaded with decomposing material. Whatever opinion one may hold, one cannot deny that the structure of a typical giant cell tumor with the abundant giant cells tied up like knots at the junctions of endothelial strands suggests that the giant cells play an important rôle in the composition of the tumor (Fig. 82). It is true that, when needed, the giant cells take up the function of scavengers and it is not uncommon to find in giant cells fatty detritus, remnants of blood cells, blood pigment, and even small spicules of bone.

Apart from giant cells one may occasionally encounter in the stroma of a giant cell tumor a lymphocytic and myelocytic infiltration which is not unusual for a medullary lesion. In tumors of long standing one sees an advanced differentiation of the fibroblastic stroma entering a cicatrizing and fibrosing stage. Such a differentiation may be hastened by radiation therapy or by a spontaneous fracture through the tumor. Usually the differentiation proceeds from the periphery to the center of the tumor but occasionally one encounters a differentiation in islands in the middle portion of the tumor while the more peripheric portions

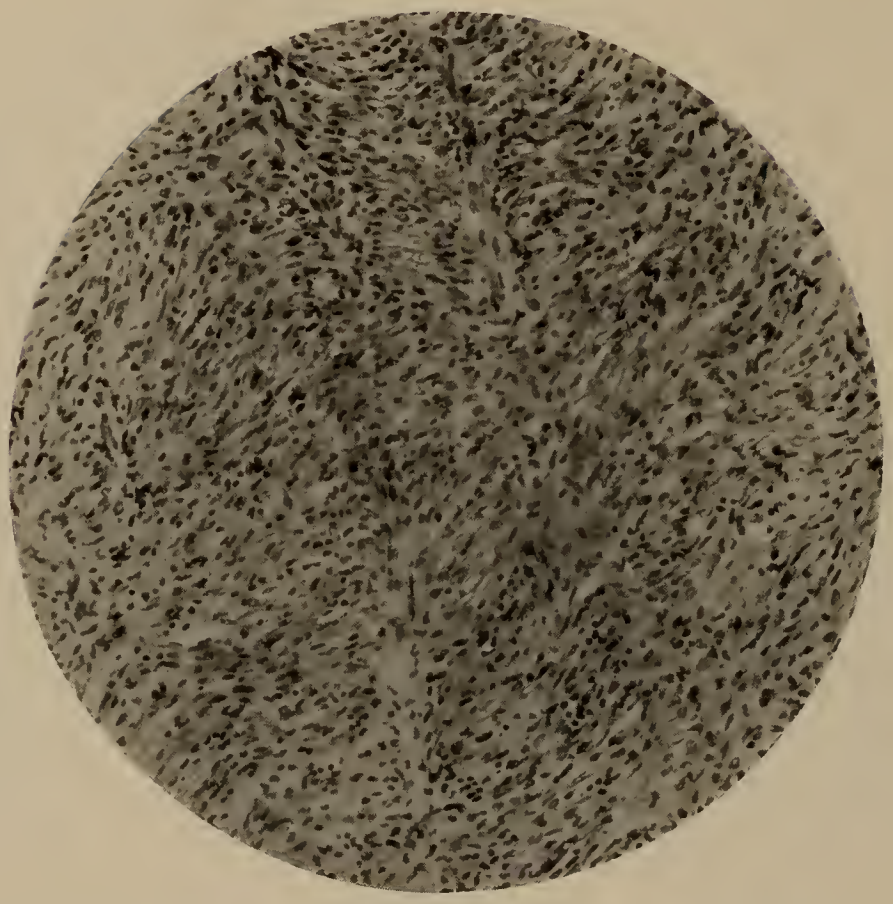


Fig. 83. Case 103. Giant cell tumor; cicatrizing and fibrosing stage. The stroma is represented by a dense fibrous tissue poor in giant cells.

temporarily remain immature. The spindle fibroblasts become smaller; fibrils appear about them, and soon the stroma is represented by a dense fibrous tissue poor in cells (Fig. 83). Osteoid tissue formation and metaplastic ossification can be expected here.

To avoid errors in diagnosing a giant cell tumor from the histology one has to keep in mind the various deviations from the typical giant cell tumor structure. Probably the most frequent variation of giant cell tumors is the so-called xanthoma, when the resorption of a considerable amount of fatty detritus leads to an impregnation of the phagocytozing cellular elements with lipoids. Typical giant cells are few there, and their place is taken by aggregates of endothelial leucocytes which are peculiar here because of the fairly granular cytoplasm resulting from the lipoid inclusions. These are the so-called "foam cells" (Fig. 84). A deviation from the typical giant cell tumor is also observed in the myxomatous variation, the peripheral portion of which consists of spindle cells, slightly smaller in size with a large chromatin content of the nuclei, embedded in a mucinous mass (Fig. 85). The central portion may retain all characteristic features of the typical giant cell tumor and even show areas of spontaneous healing with hyalinization and calcification (Figs. 86, 87).

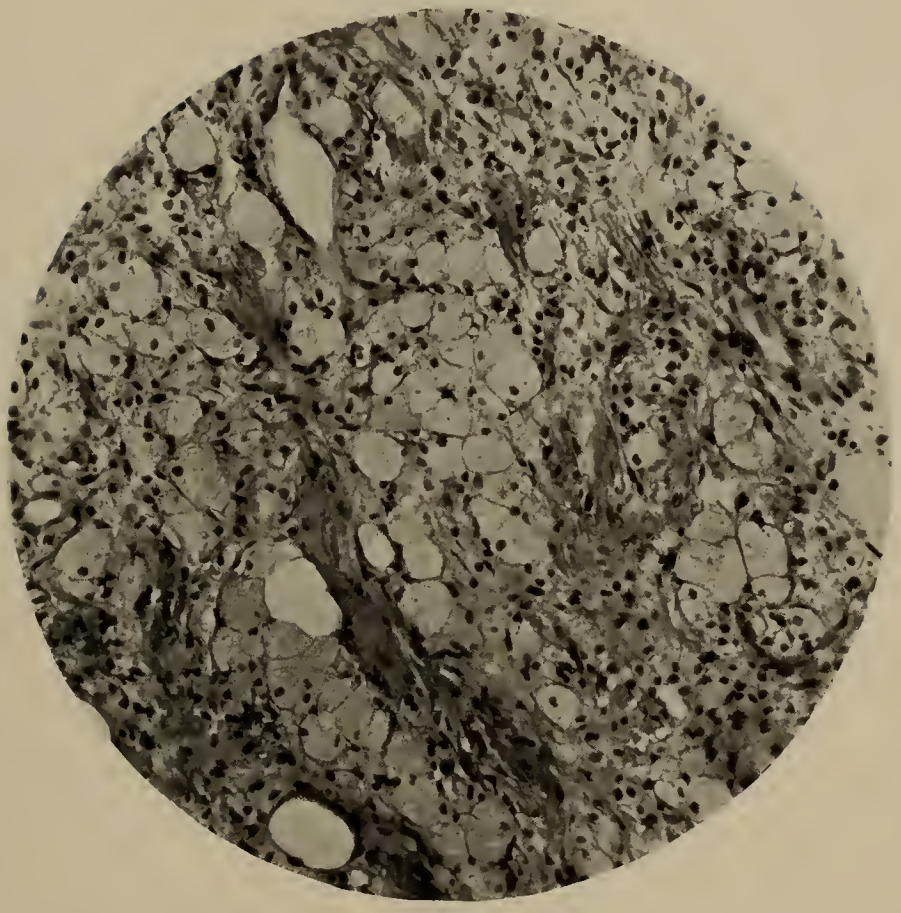


Fig. 84. Case 454. Compare with Figure 78. Giant cell tumor; xanthoma variety. Showing the "foam cells" filled with lipoid inclusions.

The variety of giant cell tumor originating in connection with an absorption of misplaced islands of cartilage, presents a marked deviation from the normal structure. Along with areas of degenerating cartilage undergoing absorption and calcification newly formed, imperfect cartilage cells can be seen as polyhedral granular cells arranged in sheets and clusters. At a glance they somewhat resemble epithelial cells and the name "epithelioid cells" has been suggested for them (Fig. 88). The degenerating cartilage is hyaline or dark staining fibrillar material. The spindle fibroblastic structure is absent here and a very cellular stroma composed of rounded cells gives the tumor the general aspect of a myeloma (Fig. 89). There are a few giant cells scattered in the cellular areas, especially about extravasations and blood spaces.

Unlike malignant bone tumors, in which the destruction of the involved bone is accomplished by both osteoclasts and tumor cells, in giant cell tumors the task of destruction of the cortex is taken over by the giant cells. The destruction of the bone shell by the giant cells from within and the apposition of new bone by a dense row of osteoblasts beneath the periosteum from without can be easily seen in section (Fig. 90). In the areas where the struggle between the giant cells

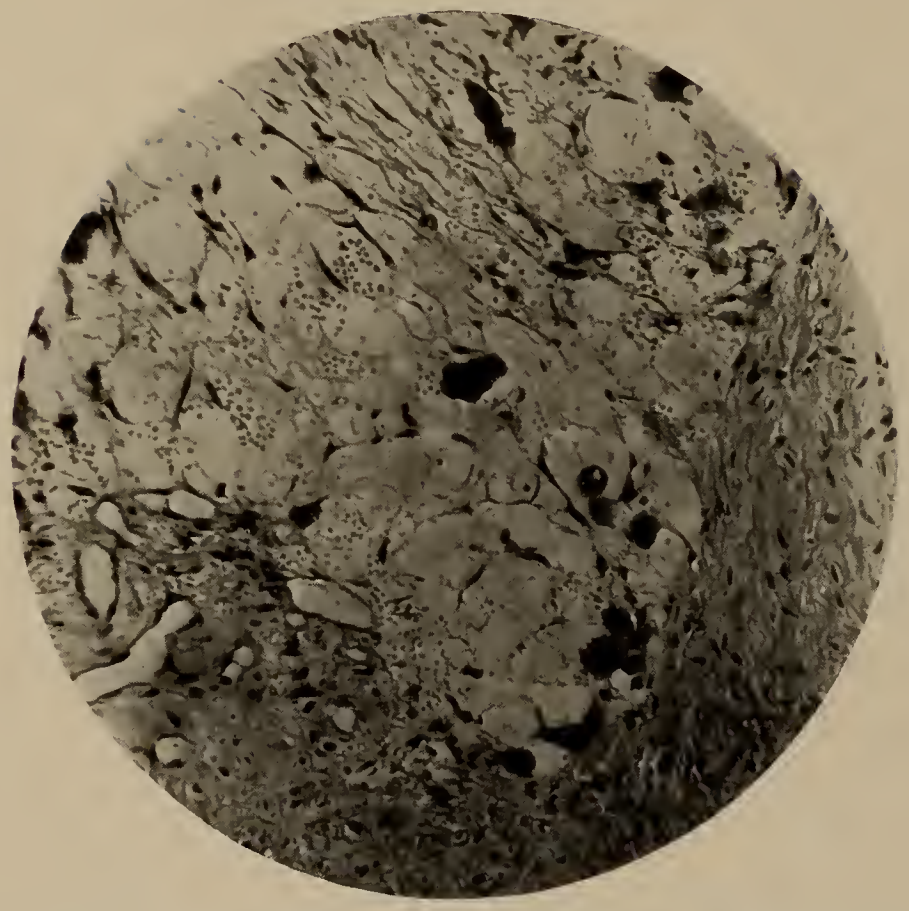


Fig. 85. Case 592. Same case as that in Figures 86 and 87. Giant cell tumor. This section was taken from the periphery of the tumor. Showing the myxomatous structure of the tumor.

and the osteoblasts resulted in a complete destruction of the bony capsule, the giant cells retreat from the advance guard of the tumor and the number of giant cells along the periosteal investing capsule is smaller than when remnants of bone were lining it (Fig. 91). The periosteum remains intact for a long time, forming the last wall of defense before the tumor breaks through into the surrounding soft tissues. Nothing contributes more to the hastening of such a perforation than an exploratory incision or incomplete curettage. Once incised the periosteal capsule remains open and disabled in its effort to encapsulate the tumor.

When a recurrence has taken place in a giant cell tumor the histology shows a variable picture and is always of an altered character. Cicatrization of a giant cell tumor may be hastened occasionally by incomplete curettage and sometimes even by an exploratory incision, provided infection does not set in. Frequently, however, infection is not avoided and the infected fungating pulsating masses of the tumor acquire an appearance of a malignant new-growth. Histologically such a giant cell tumor is greatly changed by the admixture of a reaction to infection and by stimulation to active growth.

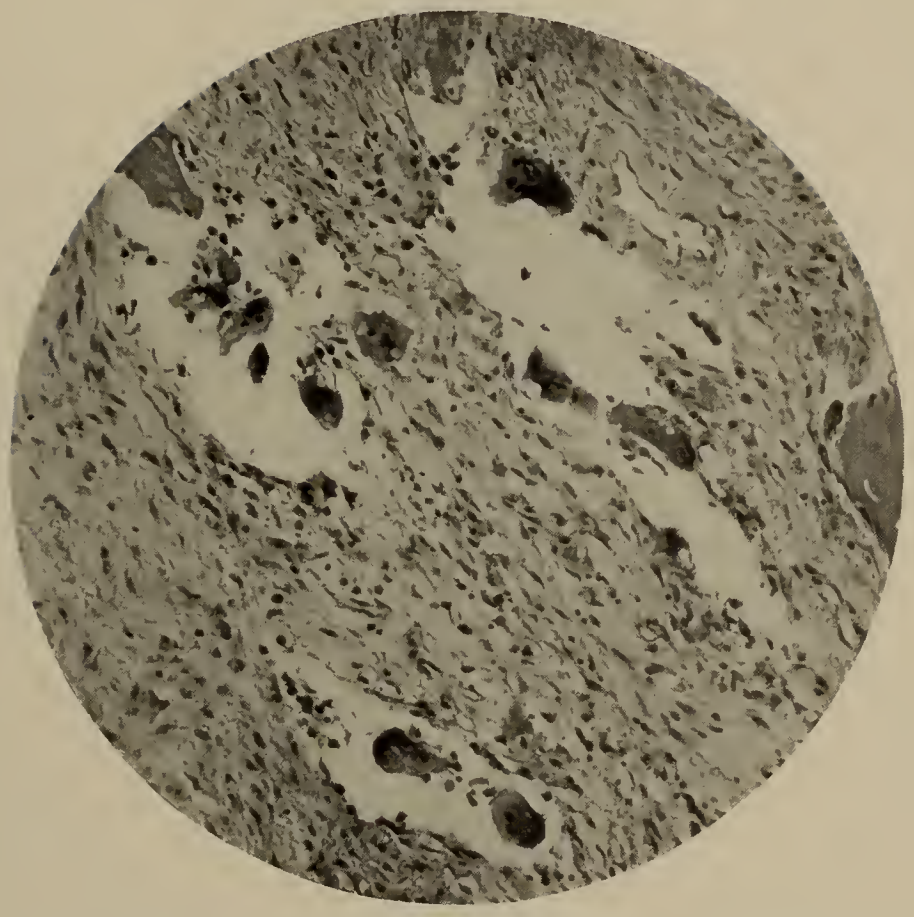


Fig. 86. Case 592. Compare with Figures 85 and 87. This section was taken from the central portion of the tumor. Typical structure of giant cell tumor.

Clinical Course

The clinical incidence of giant cell tumors is apparently lower than that of primary malignant bone tumors. If one judges from the material of the Registry, the relative frequency of giant cell tumors as compared with malignant bone tumors is about 1:2. This ratio is probably an exaggeration of the frequency of giant cell tumors, since the Registry material counts many cases in which the patients were alive at the time the Registry began, while the average life duration of a patient with a malignant bone tumor is about 20 months. The giant cell tumor is more frequently met with in the female than in the male; the ratio 6 to 5 is probably a fair expression of this frequency. The age in which giant cell tumor is most frequently encountered is expressed by the adjoining histogram (Fig. 92). It is in the decade between 16 and 25 that most giant cell tumors occur, an age considerably higher than for osteogenic sarcoma and Ewing's sarcoma. In 28 per cent of females the disease occurred after the age of 30 as against 41 per cent in males. The youngest patient was a girl of 6 and the oldest a man of 68.

The location of the giant cell tumor is in marked contrast to that of osteogenic sarcoma as far as the bone and the site of involvement is concerned. The bones of

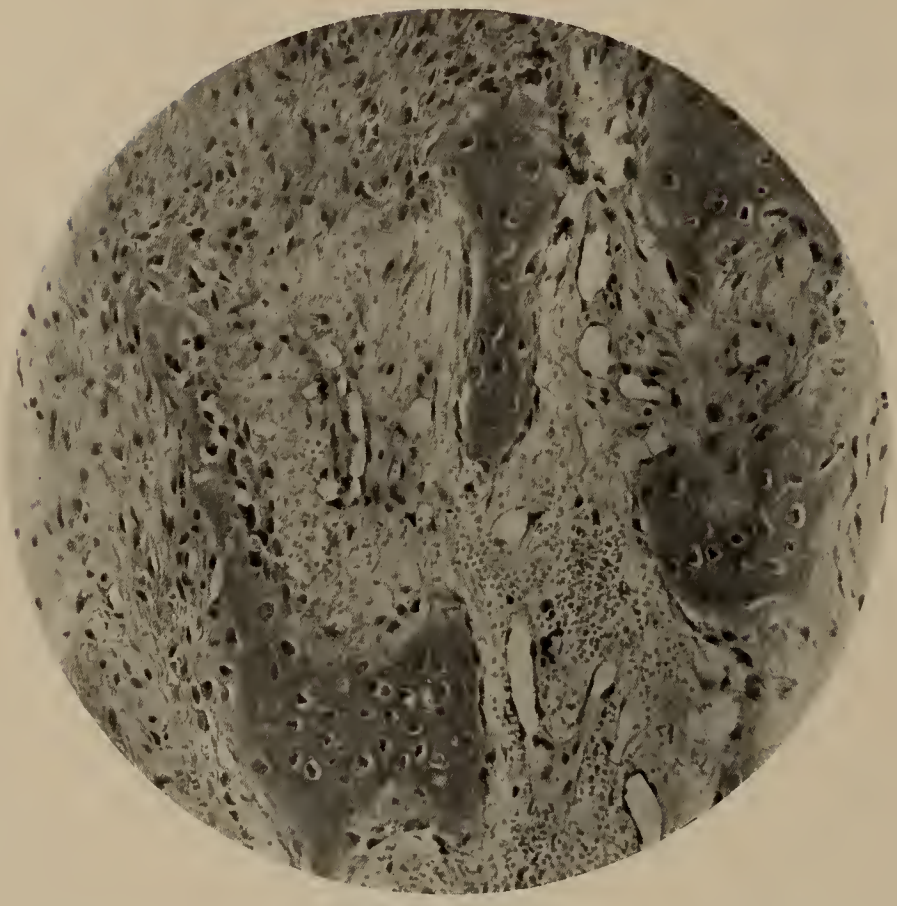


Fig. 87. Case 592. Compare with Figures 85 and 86. Showing areas of spontaneous healing with hyalinization and calcification.

the lower extremity were involved in 56 per cent of all cases of the Registry while those of the upper extremity were involved in 23 per cent of all cases; in 21 per cent of all cases the bones of the trunk including the pelvis and shoulder girdle and the jaws were involved. Of all the cases of involvement of the upper extremity the radius was involved in 40 per cent, all in the lower end of the bone. The femur was involved in 57 per cent of all cases of giant cell tumor of the lower extremity and the tibia in 36 per cent. The lower end of the femur was, as a rule, involved, with very few exceptions, when the tumor was situated in the upper third of the femur about the trochanters. The lower end of the femur is involved much more frequently in the male than in the female while an involvement of the upper end of the tibia, which is three times as frequent as that of the lower end of this bone, is seen more frequently in women than in men. In general in about 47 per cent giant cell tumors were situated in the lower end of the femur and the upper end of the tibia. The jaws were the seat of the tumor in about 9 per cent of all cases, the spine following closely with 8 per cent of all cases of involvement. Involvement of the jaws which is equally distributed between the upper and lower jaw, is apparently rare after the age of 25. The shaft of the long bones was involved in two cases, while in both these cases there was place for doubt as to the

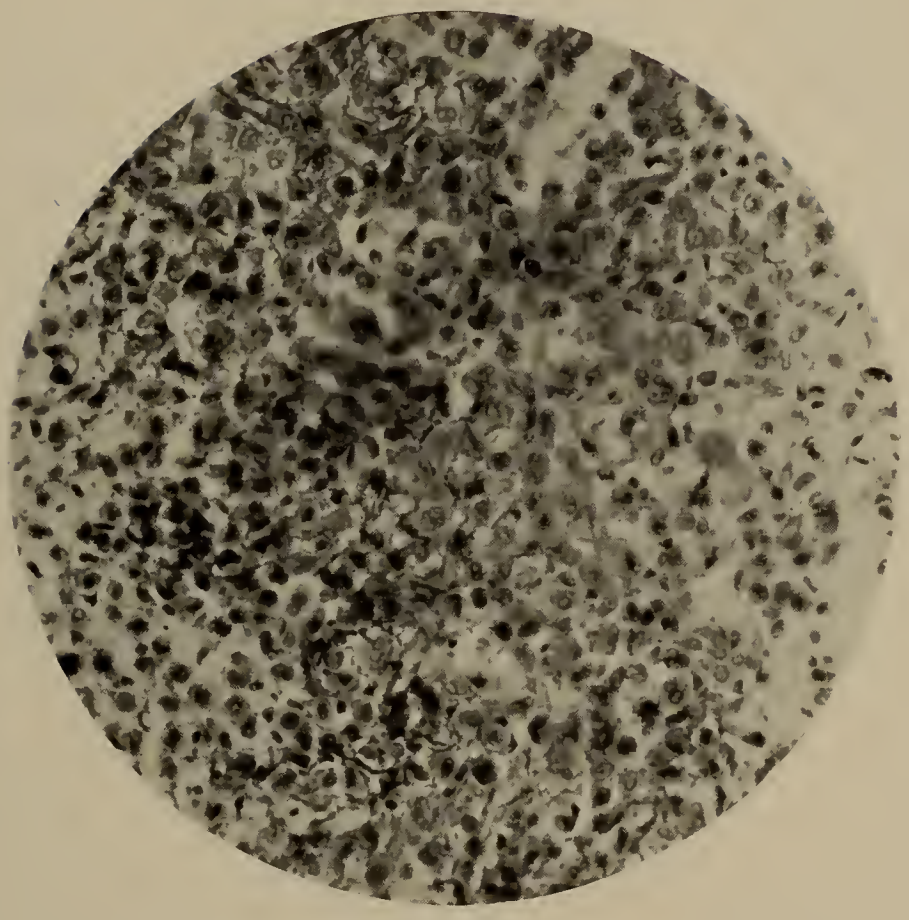


Fig. 88. Case 5. Same case as that in Figures 89 and 98. Giant cell tumor. Showing the "epithelioid cells."

accuracy of the diagnosis since a cyst complicated by fracture could not be ruled out. Giant cell tumor is situated in the small bones of the extremities more frequently than osteogenic sarcoma. In contrast with osteogenic sarcoma, in which the epiphysis frequently escapes involvement because of the epiphyseal cartilage serving as a barrier to the spreading tumor, in giant cell tumor the epiphysis is involved in the large majority of cases. Here the epiphyseal cartilage does not seem to exert any influence upon the spreading of the tumor and the latter frequently extends from here into the diaphysis. When the tumor is situated in the lower end of the femur or the upper end of the tibia, frequently one condyle or one tuberosity is involved; the tumor may spread into the diaphysis leaving the opposite condyle or tuberosity uninvolved. As a rule the giant cell tumor appears as a solitary lesion and it would seem probable that in some of the cases of multiple giant cell tumors one is dealing with a proliferative osteitis fibrosa.

The importance of trauma as an etiological factor in giant cell tumor has been mentioned above. If one is careful in gathering the facts of the patient's history, one very frequently encounters an antecedent local injury. In giant cell tumor of the jaw it is not uncommon that after a loose tooth is pulled a giant cell tumor develops; in such cases the injury apparently plays a stimulating rôle in the growth

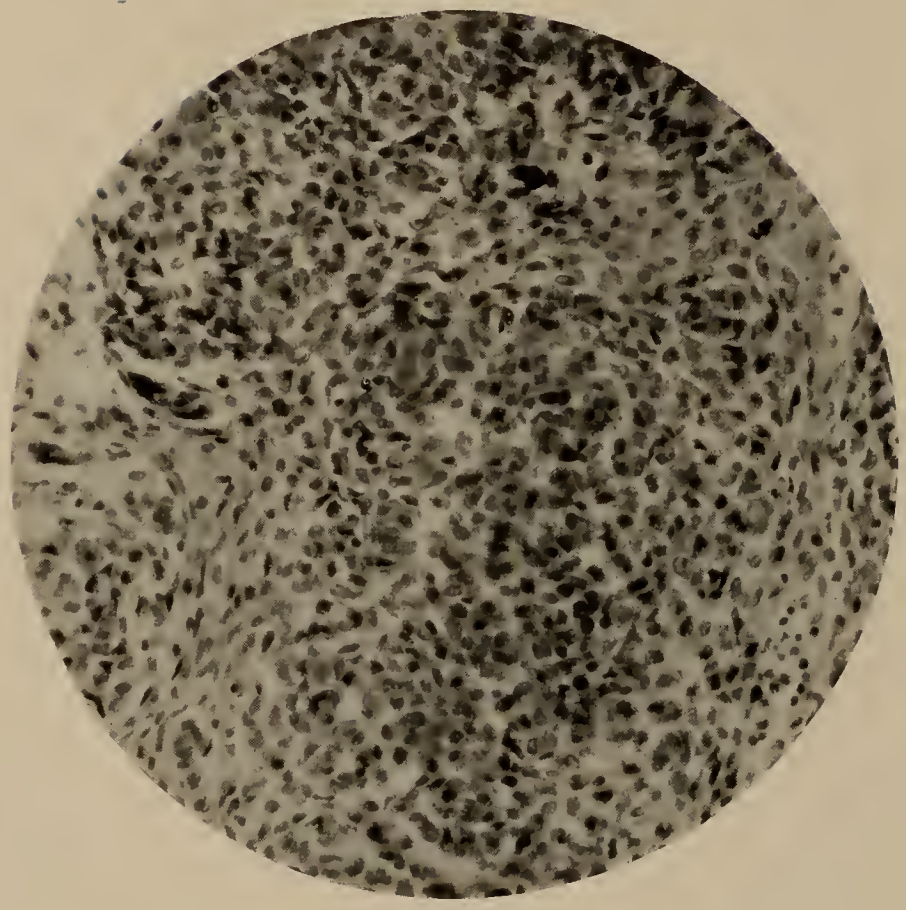


Fig. 89. Case 5. Compare with Figures 88 and 98. The cellular stroma consisting of round cells reminds one of myeloma.

of the tumor. Pain is frequent and early complained of by a patient afflicted with giant cell tumor. The pain, however, is of less severity than in osteogenic sarcoma, and it is more persistent after radiation therapy is begun. The patient's general condition usually remains good unless an exploration or incomplete curettage was done accompanied by infection. Infection is very persistent in giant cell tumor and it may lead to sepsis in a brief period of time. The skin frequently lacks the dilated veins commonly seen in osteogenic sarcoma. When the skin is very distended by the large tumor, it may resemble pig skin, be œdematous and cyanotic. Ulceration of the skin occurs apparently only in the very far advanced cases which have long gone without medical attention.

Palpation is an important diagnostic aid in the examination of a giant cell tumor. Frequently one is able to palpate the bony capsule of the tumor and its borders at the junction with the uninvolved diaphysis. One feels the bulky spheric shape of the tumor as contrasted with the fusiform shape of the osteogenic sarcoma. It is much easier to palpate in giant cell tumor because of relative absence of tenderness. When the bone shell of the tumor becomes very thin, egg-shell crackling can be made out. In the very vascular variety of giant cell tumors one occasionally feels a bruit. As a rule giant cell tumor is of long duration

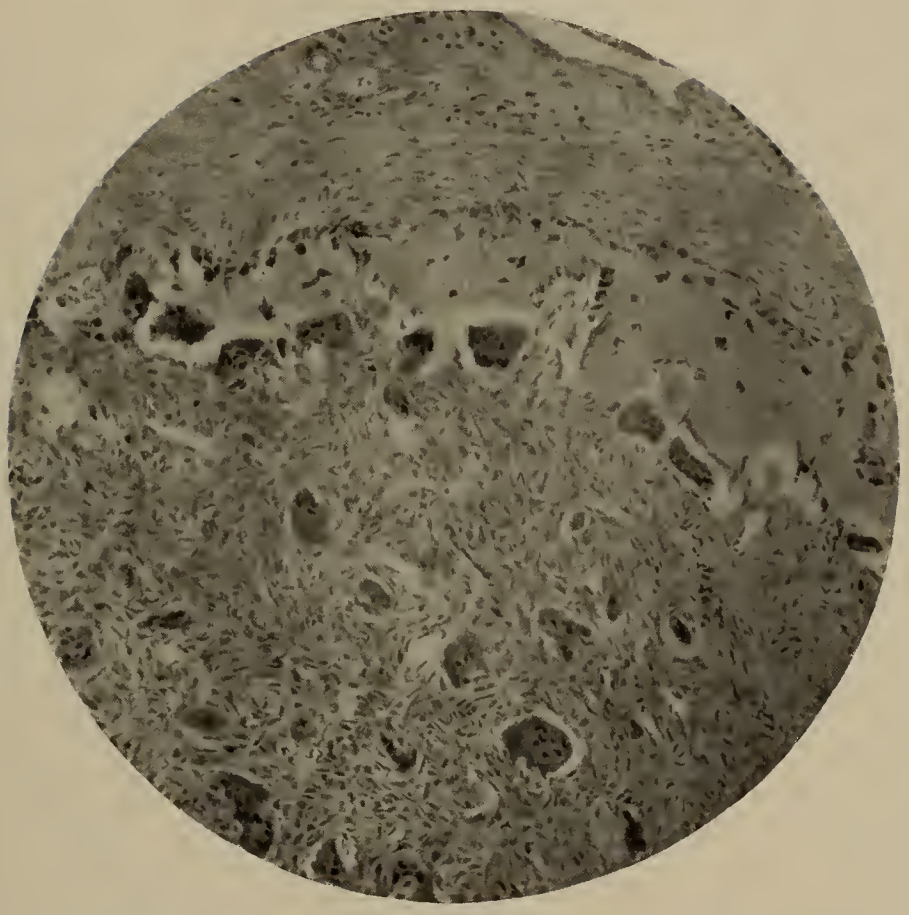


Fig. 90. Case 235. Same case as that in Figure 91. Giant cell tumor. Showing the destruction of the bone shell by the giant cells from within and the apposition of new bone by rows of osteoblasts beneath the periosteum.

and slow growth; notable exceptions are known however. At the present day advanced stages of giant cell tumors are seldom seen since their growth is interrupted by surgery or radiation. Occasionally in long standing tumors attempts at spontaneous healing occur,—cicatrization with ossification of the peripheric portion and cyst formation in the center. When infection takes place fatal hæmorrhage and sepsis may ensue. After breaking through the investing capsule the tumor travels along the intermuscular and fascial planes but does not invade the muscle tissue. In giant cell tumors of the spine a compression myelitis may offer an orthopedic issue. Frequently such patients die from supposed sarcoma while occasionally they can be saved by orthopedic measures. Infraction is almost a rule in giant cell tumor, especially in the weight bearing bones, where also complete pathological fractures are frequent. This fact again emphasizes the necessity of splinting and recumbency. The pathological fracture of the lower extremity is usually of the telescoping variety, with one end of the bone projecting into the cystically dilated other end. Joint involvement is exceedingly rare. When it occurs it frequently is due to undermining of the articular cartilage, which process is followed by collapse of the joint and rupture of the tumor into it.

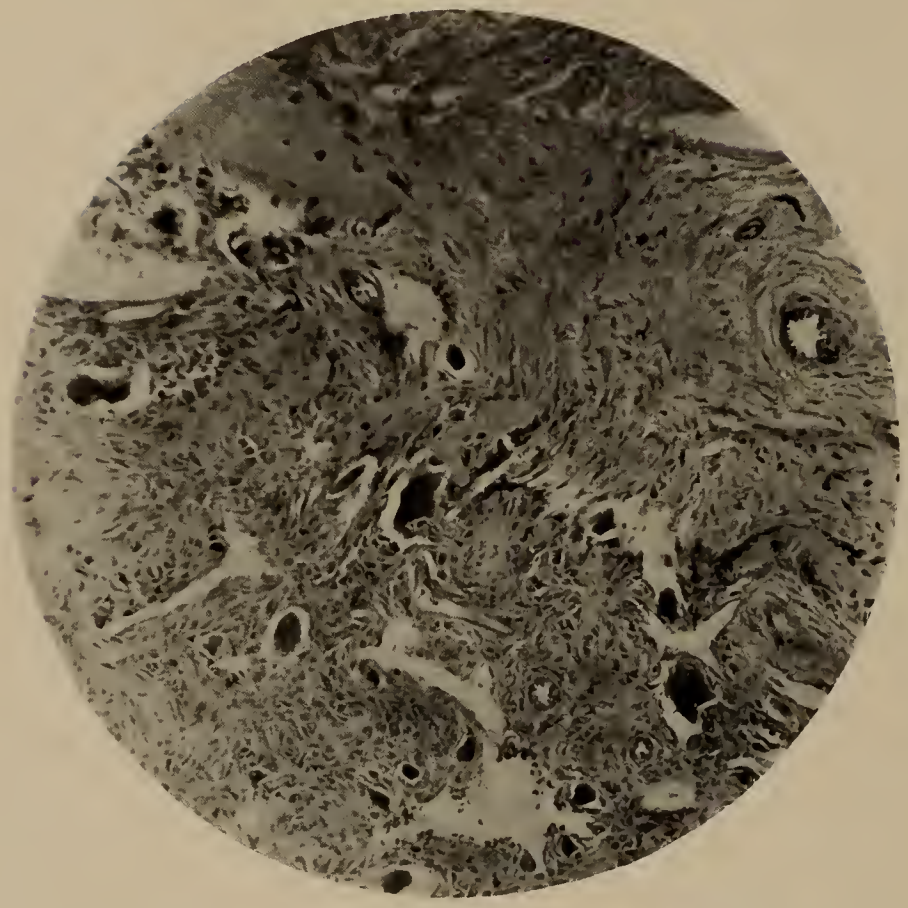


Fig. 91. Case 235. Compare with Figure 90. When the bone shell is destroyed the giant cells retreat from the advance guard of the tumor, and the number of giant cells along the periosteal investing capsule is scarce.

Diagnosis

Most of the general points in diagnosis outlined in the chapter on osteogenic sarcoma are applicable also in relation to giant cell tumors. While some experienced observers maintain that it is always possible to arrive at a diagnosis in giant cell tumor from a microscopic examination of the section alone, and others claim that the clinical history together with the physical findings and roentgen-ray features will suffice for diagnosis without an exploration of the tumor, there are times when neither method of examination, clinical and radiological, or microscopic, nor both of them combined will suffice for an accurate diagnosis. These cases are rare, frequently they are complicated by previous surgical treatment. These are the cases referred to by Ewing as the "borderline" giant cell tumors, with a wide destruction of bone, with an absence of the bone shell with smaller than usual giant cells containing larger and more hyperchromatic nuclei; they present a difficult task for the pathologist especially when diagnosis is requested from small curetted pieces of tissue. It is with reference to these cases that Platou said: "It is deplorable that a microscopic examination sometimes permits only of a probable

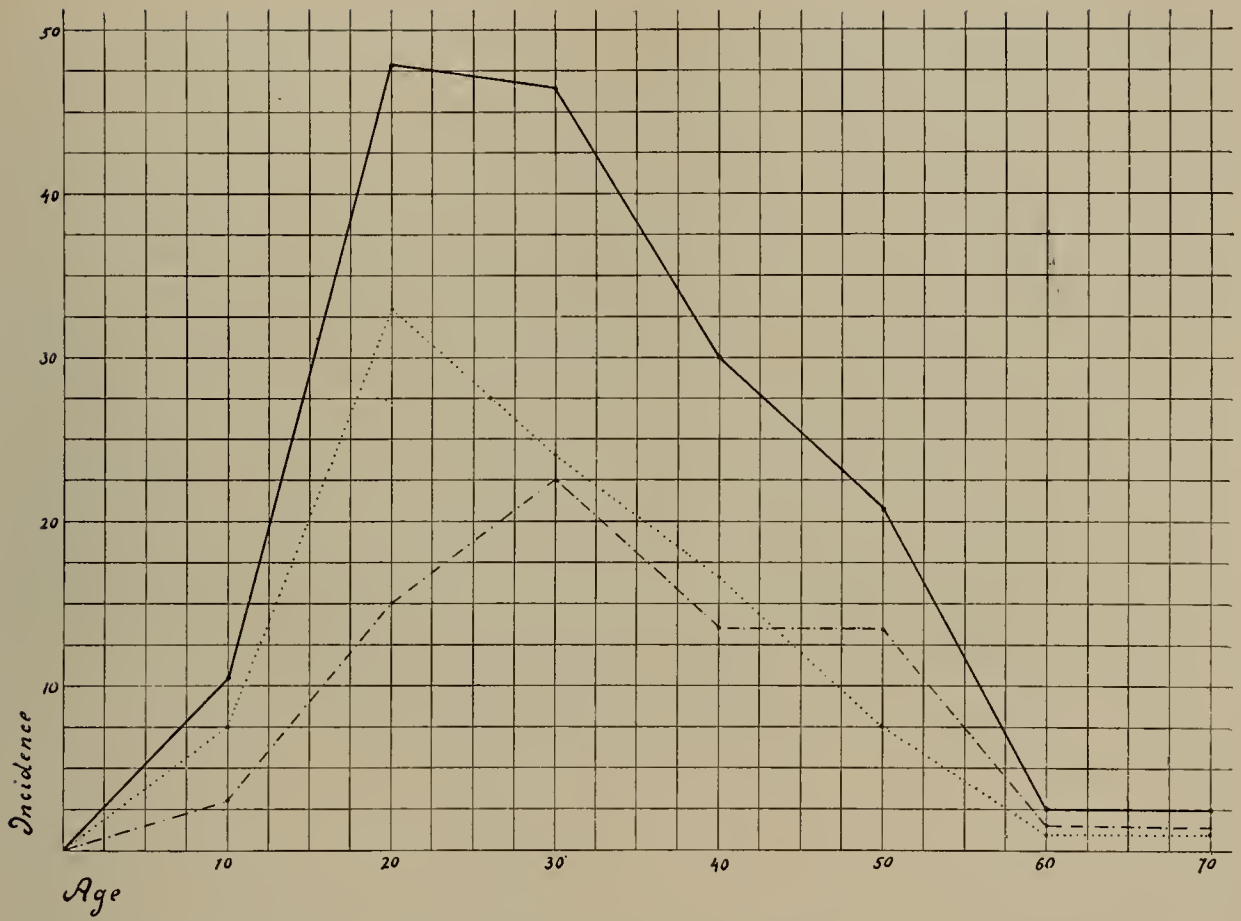


Fig. 92. Curve illustrating the incidence of giant cell tumor in relation to age. Dotted line—females; broken line—males; heavy line—both sexes combined.

diagnosis." Despite this fact it should not be understood that in general the diagnosis of giant cell tumor requires all available data together with an exploratory incision. To the careful observer a complete history and thorough physical examination, supplemented by satisfactory roentgenograms, will suffice for an accurate diagnosis in the majority of cases.

In attempting a diagnosis of giant cell tumor from the clinical findings alone, one should remember that the most frequent error is mistaking it for osteomyelitis; this is at least not less frequent than mistaking it for an osteogenic sarcoma. Because of the location of giant cell tumor in the ends of long bones and also because of its long duration and slow progress, it is the tuberculous osteomyelitis and the tuberculous joint involvement with which one is mostly concerned in such cases. This is especially true when, as it frequently happens, the giant cell tumor is situated about the knee joint. The asymmetric enlargement of only one side of the region of the knee joint and not of the whole area as in tuberculosis, and the absence of the fusiform swelling of the joint, which is frequent in tuberculosis, are strong differentiating points. To depend entirely upon the laboratory specific tests for tuberculosis is not recommended because of their frequent failure as an accurate diagnostic means. In a patient who later died of an osteogenic sarcoma

Plate 38. Courtesy of the Ruptured and Crippled Hospital, New York City. Primary sarcomatous tumor of the spine. The tumor arose in the tenth dorsal vertebra which is extensively destroyed while the intervertebral discs remain intact.

without evidence of tuberculous involvement at autopsy, I have seen, following an intradermal tuberculin injection, a positive local, focal, and general reaction. Giant cell tumor of the spine is frequently confounded with tuberculous spondylitis. Nervous disturbances as a result of pressure on the spinal cord and nerve roots are likely to appear earlier in a tumor involvement than in tuberculosis. The pain is of more or less intermittent character in the beginning of the disease and abscesses are absent even in well advanced stages of the tumor. While in Pott's disease the intervertebral discs are destroyed early, in giant cell tumor and also in osteogenic sarcoma and Ewing's sarcoma the destruction of the vertebral body greatly precedes that of the discs (Plate 38). Another sign of giant cell tumor of a vertebra, which is especially significant in the presence of a malignant tumor, is œdema of the soft tissues overlying the involved area of the spine.

The outstanding diagnostic importance of the radiological examination goes without saying. To be of real value and not misleading, the roentgenogram must be irreprehensible. All the important technical points mentioned in the chapter on osteogenic sarcoma are true also here. Repeated radiological examination of skeletal tumors from many angles is indispensable for an accurate diagnosis. The roentgenogram is frequently of more importance than a microscopic examination when a variant of giant cell tumor is dealt with; so for instance in cicatrizing giant cell tumor the histology will be that of a fibrosarcoma but the roentgenogram will be typical of a giant cell tumor.

The radiological appearance of a giant cell tumor is most characteristic (Figs. 93 to 100). It usually casts a bulky spherical shadow showing a multicystic

Fig. 93. Courtesy of Memorial Hospital, New York City. Typical roentgenogram of a giant cell tumor.

appearance as a result of the osseous trabeculation in the periphery. The shaft of the bone is absent and it appears as if the cortex is blown out from within the medullary cavity so as to form the thin bone shell, which sharply limits the tumor from the surrounding soft tissues. Beyond the tumor the cortex and the periosteum are entirely unaffected and no periosteal lipping is seen. In the clear roentgenogram an apparent continuation of the bone shell is seen limiting the tumor from the adjointing unaffected medullary cavity; this shadow is an important diagnostic feature and deserves much attention. Not infrequently this borderline shadow is not seen in the roentgenogram because of unsatisfactory technique. To show it requires care in adjusting the position of the tube in relation to the tumor and a rather exacting localizing technique. When the diaphyseal end of the tumor is brought into the field of central rays of the tube it is rarely missed. When in advanced cases of giant cell tumor the bone shell is destroyed, in some areas the roentgenogram will simulate an invasion of the tumor into the soft tissues in spite of the intact periosteum; it should be remembered, therefore, that such a break in the continuity of the bone shell is not a sign against giant cell tumor. When the whole bone shell is destroyed it may be difficult to differentiate it from osteogenic sarcoma but frequently roentgenograms from various angles together with palpation and the clinical history will help in the diagnosis. The fact that the adjoining periosteum and cortex remain unaffected speaks strongly against osteogenic sarcoma. Usually one or another view of the tumor in the roentgeno-

Fig. 94. Courtesy of Memorial Hospital, New York City. Typical giant cell tumor.

gram will show in osteogenic sarcoma the shaft running in the tumor, while in giant cell tumor the shaft is absent. An important differentiation point is also the fact that in osteogenic sarcoma the tumor does not reach the articular cartilage, a layer of spongiosa a millimeter or two in thickness remaining between the tumor and the cartilage, while in giant cell tumor, the tumor is in direct contact with the cartilage. Another condition which requires ruling out in the diagnosis of giant cell tumor is bone cyst. In the majority of the cases this is, however, not difficult. A cyst is intra-osseal and expands the bone only slightly. The cortex of the bone at both poles of the cyst is thinned out so that there is gradual thinning of the cortex from the poles to the middle of the cyst and not an abrupt transition of the normal cortex in a greatly expanded thin trabeculated shell as in giant cell tumor. A cyst is mostly located in the shaft, while a giant cell tumor is in the ends of long bones. The situation of the tumor is not infrequently decisive; if a tumor is in the condyle of the femur or in the tuberosity of the tibia and before breaking through the shaft it extends into the diaphysis, a giant cell tumor is to be considered. It is generally believed that in children a spontaneous fracture as a symptom of onset in a central lesion is characteristic of a cyst and not giant cell tumor. Occasionally a far advanced fibrocystic lesion, when it expands to the epiphyseal and of the bone, may suggest a diagnosis of giant cell tumor. However, in osteitis fibrosa cystica, while the involvement extends far along the shaft, it is not accom-

panied by a corresponding expansion of the bone in transverse diameter, as is seen in advanced giant cell tumor. Osteitis fibrosa is more apt to occur in old than in young people (Figs. 101, 102).

When combined with the clinical history, physical findings and radiological features, the data of a pathological examination are of valuable diagnostic importance. The main sources of error in the diagnosis of giant cell tumor from the histology should be mentioned here. It may be safely argued that to one experienced in the pathology of bone tumors the gross anatomy of a giant cell tumor will frequently mean more than the histology, and a diagnosis from the gross specimen will be more apt to be accurate than when the diagnosis is based upon the slides alone. It is well to remember that an occasional tumor, however, can resemble grossly or histologically a giant cell tumor and not be one. The histology is frequently misleading in giant cell tumor; especially so when a frozen section is relied upon, as often happens. The diagnosis of giant cell tumor from the section must not be based upon the presence of giant cells alone; the type of the supporting tumor cell is most important. Although the giant cells are an integral part of the giant cell tumor they are occasionally encountered also in typical osteogenic sarcoma where lime salts are set free by rapid erosion and disintegration of bone. This fact is not realized sufficiently by the average surgeon and pathologist who have only a casual acquaintance with the pathology of bone tumors, and it is a con-

Fig. 95. Courtesy of Memorial Hospital, New York City. Typical giant cell tumor.

Fig. 96. Case 295. Same case as that in Figure 97. Giant cell tumor in a man 25 years old. This roentgenogram was taken at the time of onset.

stant source of grave errors. Another fact which is not sufficiently realized is that very vascular, so-called telangiectatic osteogenic sarcoma may resemble grossly vascular giant cell tumor. There also one finds giant cells of the epulis type about extravasations. The histology is not infrequently misleading in the variants of giant cell tumor. So, for instance, in the myxomatous variation the histology may suggest malignancy while the clinical findings and radiological features clearly indicate the benign nature of the lesion. In cartilaginous giant cell tumors in a few cases a diagnosis of myeloma has been returned by the pathologist because of the abundance of rounded cells of the stroma. The advanced cicatrizing stage of giant cell tumor may suggest fibrosarcoma, if other data are disregarded. Occasionally several variants may be found in the same tumor. The histology is especially deceiving when the tissues were taken from tumor masses fungating through a former exploratory incision. It is extremely hazardous to base a diagnosis on findings from these granulation tufts. The numerous mitoses here are mostly in the endothelial leucocytes.

The question of indication and contra-indication of biopsies in giant cell tumor is still under discussion. It would seem that the whole question is merely a part of the general problem of the advisability of a biopsy in bone tumors of doubtful nature, since the necessity of exploration indicates that one is not certain whether the tumor is benign or malignant. The difficulties encountered in a diagnosis from the histology in a doubtful giant cell tumor are great and insurmountable to those little initiated in the pathology of bone tumors. As a general rule, when the clinical findings and the roentgenogram are baffling to the clinician, the histology is also distressing to the pathologist. Whatever one may say about the possibility of increase of malignancy in giant cell tumors by an exploratory incision one cannot deny that the dangers of infection with which such explorations are

Fig. 97. Case 295. See Figure 96. This roentgenogram was taken 1 year after the onset. At that time radiation therapy was instituted which led to a shrinkage of the tumor. The patient is earning his living. This is the largest giant cell tumor in the Registry collection. The radiological features are typical of giant cell tumor.

entailed are very great. The spongy vascular tumor and the exposed bone-marrow are very susceptible to infection, and a cellulitis, suppurative osteomyelitis and septicæmia are not rare after such procedures. However, if a biopsy is done the curettage of the tumor should be completed because a following infection will add greatly to the difficulties of radiation. To be decisive a biopsy should include all parts and not only the periphery of the lesion. The radiation therapeutic test is not of such great importance in giant cell tumor as in osteogenic sarcoma

Fig. 98. Case 5. The same case as that in Figures 88 and 89. Giant cell tumor in a boy of 16. The trabeculation in a giant cell tumor of the upper end of the humerus is usually of a more delicate structure, the involved bone appearing honeycombed.

and especially in Ewing's sarcoma however, we have a differentiating point in the fact that pain in giant cell tumor persists after radiation is begun, while in malignant tumors it is usually relieved sooner. In the rare case of an aggressive, rapidly growing tumor which has reached a far advanced stage when first seen, radiation and perhaps an exploratory incision would seem to be better justified than a direct amputation of the limb with only a probable diagnosis of malignancy in one's mind.

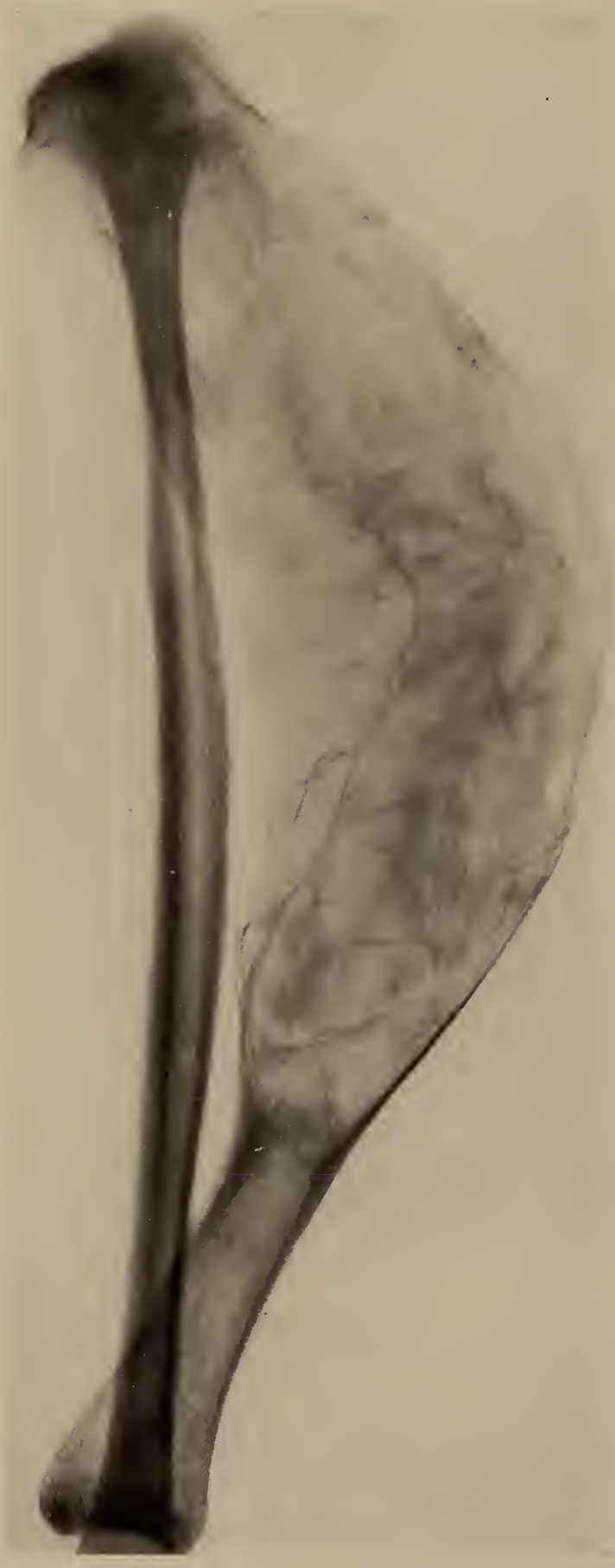
Therapy

While in malignant bone tumors the problem of therapy today is to find a way to relieve the sufferings of the patient for a longer period of time, in giant cell tumor the whole crux of the question is as to choice between various methods of treatment, each of which may lead to permanent cure. The history of the therapy of giant cell tumor is remarkable for the continuous change from radical to more conservative methods of treatment. The almost universally employed amputation of some twenty-five years ago was followed by partial resection which later gave way to curettage; and it was curettage that constituted the standard method of therapy in giant cell tumor until very recently. That spontaneous cures of giant cell tumor occur is sufficiently attested; such instances are probably more frequent than is suspected. Toxin treatment has not been applied as frequently as in malignant bone tumors, the adepts in this method of treatment advocating the use of toxins merely as a prophylactic along with radiation after incomplete surgical operations.

Fig. 99. Case 542. Giant cell tumor in a woman of 49. The seat of the tumor in the lower end of the ulna is uncommon, the lower end of the radius being the favored seat of a giant cell tumor about the wrist.

Fig. 100. Case 195. Benign osteogenic tumor. The presence of the shaft of the bone and the fact that the tumor is extracortical speaks against giant cell tumor; the clear cut outline of the tumor speaks against osteogenic sarcoma.

The most frequently employed method of curettage consists of the following procedure: curettage of all removable portions of the tumor followed by swabbing out of the rough curetted area with pure carbolic acid and alcohol, or as some advise, with zinc chloride. The subsequent packing of the cavity with gauze to



prevent hæmorrhage has been given up by some men, who close tightly the operative wound expecting an organization of the blood clot. A promiscuous use of this device in all cases of giant cell tumor should be warned against, since fatal hæmorrhages are known to have occurred. On the other hand if one packs the cavity with gauze, infection is frequent notwithstanding all preventive measures. Whatever the way of dealing with the cavity, the limb should be immobilized to prevent a pathological fracture which will still further complicate the course.

As a prophylactic against a recurrence, radium therapy is to be recommended. Recurrence seems to be frequently unavoidable and is observed in about 20 per cent of all cases treated by a single curettage alone. The cause of recurrence is not known. The histological structure of the tumor gives little explanation of this. The question whether the bone shell is intact or not does not seem to be the decisive factor. That the completeness of curettage has little to do with

Fig. 101. Courtesy of Warren Museum, Boston. Osteitis fibrosa of the tibia in a man of 87. The line of demarcation from the normal bone; the newly formed trabeculæ, the effort of nature to form a buttress behind the bent portion; the intact periosteum and the bowing of the bone are all typical of advanced osteitis fibrosa. Amputation was performed in 1872 by Bigelow.

Plate 39. Case 319. Giant cell tumor in a man 38 years old. Onset in September, 1922. Roentgen-ray irradiation on October 26 and 28, 1922, and on March 13 and 23, 1923. The roentgenograms were taken: October 15, 1922; January 15, 1923; April 18, 1923; May 21, 1924. Function of wrist completely restored.

Fig. 102. Personal observation; not registered. Osteitis fibrosa cystica in a man 68 years old. The lesion was mistaken for a malignant tumor and radiation therapy instituted. Because of an ensuing pathological fracture amputation was done; the histology proved the lesion to be a typical osteitis fibrosa. The wide extent of bone involvement with the relatively small expansion of the bone suggested the diagnosis of osteitis fibrosa from the roentgenogram.

the tendency of the tumor to recur is indicated by the fact that occasionally completely curetted tumors recur while those incompletely curetted go on to a permanent cure. That cauterization is effective only to a relatively small depth is obvious from the chemical coagulative action of the escharotic. In the light of these facts one can never be certain that curettage will not be followed by a recurrence of the tumor. An even greater disadvantage of curettage is infection. This serious complication has occurred in good technical hands and under the best of conditions. The seriousness of infection in a giant cell tumor has been mentioned above. A proven potential danger of repeated curettage of a giant cell tumor is the surgical trauma by itself. I am referring later to the possibility of malignant transformation in rare instances of giant cell tumor after repeated surgical operations and infection.

It has long been known that radiant energy is an active factor as a prophylactic against recurrence of a curetted giant cell tumor. Radiation has for years been used also when the tissue removed during incomplete surgical operations in cases of giant cell tumor seemed to be suspicious. Experience has shown that if radiation is used after curettage no recurrence follows, but the cavity left after curettage does not fill in with new bone and surgery may be the final issue. More disappointing is the experience with radiation therapy of recurrence after curettage. The patient is usually promptly relieved of pain; the infection is checked soon but the growth itself is more refractory to massive radiation. Little bone repair is seen, the scar from the previous operation and even the skin may break down and add considerably to the difficulties of radiation. If curettage has been chosen and done, t should be done repeatedly f recurrences take place, and if necessary, amputation should be considered rather than a change to radiation. Men of wide experience with radiation therapy of giant cell tumor decidedly state that an incomplete surgical operation in giant cell tumor is worse than none.

During recent years a further and most significant step has been taken toward conservative treatment of giant cell tumor; it consists of substituting radiation therapy, either roentgen ray or radium, for surgical operations. It is true that the use of radiation as a primary therapeutic measure in giant cell tumor is not yet widely adopted but the experience accumulated in a few leading medical institutions, especially at the Memorial Hospital in New York, is of such weight that it eliminates any doubt as to the very great value of radiation therapy as a primary therapeutic measure in giant cell tumor, and cases of giant cell tumor cured by radiation are on record. In the reaction of a giant cell tumor to effective radiation therapy one can distinguish two opposite phases. During the first three or four months of radiation therapy the giant cell tumor increases in size, the bone shell expands greatly, becomes thin and finally melts away entirely, the skin becomes reddened, œdematous, inflamed, sore to the touch, and the whole appearance indicates a rapid growth of the tumor. The tumor acquires very suggestive

Plate 40. Courtesy Memorial Hospital, New York City. Giant cell tumor. The roentgenograms were taken (left) before radiation therapy was begun and (right) 3 years and 8 months later.

marks of a malignant sarcoma. This excessive reaction with bone absorption may be avoided by using a less severe radiation dosage. The preliminary reaction of the tumor to radiation is the destructive or negative phase in contrast to the final productive or positive phase of reaction. The latter is characterized by a constant shrinkage of the tumor and by formation of new dense bone. In contrast to the soft and pultaceous consistency of the tumor during the negative phase, it becomes gradually harder in the positive phase of reaction as a result of abundant calcium deposits (Plates 39, 40 and 41). The younger the patient and the more superficial the situation of the tumor the more prompt will be the reaction. In the opinion of those with widest experience, external radiation with roentgen ray or a radium pack is far superior to internal radiation when radium needles are placed into the tumor substance. It is also conceded that the roentgen ray is to be preferred to radium. It is especially dangerous to use unfiltered radium in tumors after curettage; in general, burying unfiltered radium within tumor tissue may lead to bone necrosis, chronic osteitis with abundant sloughs, and infection. The dangers of overradiation should not be underestimated even when external radiation alone is used, when in exceptional cases exposures extending over many months may be followed by radiation changes in the soft parts surrounding the tumor, which may lead to ulceration of the skin, and, in extreme cases, to osteitis with agonizing pain, which may require amputation.

Even if, at the present time, radiation therapy has not as yet become the standard therapy of giant cell tumor there are cases in which only radiation therapy should be considered. This is the case in the giant cell tumor of the spine and in the rare instances of giant cell tumor of the skull. In such cases no complete surgical operation is possible, because of the tendency of the tumor to widely involve the fibrous dense tissue and also of the possibility of a fatal hæmorrhage ensuing after an attempt at surgical removal.

Although the general tendency in recent years has been to substitute conservative surgical procedures and radiation for the radical amputation, the latter, however, cannot be entirely avoided in some rare instances. Occasionally the possibility of a better practical result will decide for amputation rather than curettage. This is sometimes observed when the tumor is situated about the knee, or ankle joint. Infection after biopsy and curettage with suppurative osteomyelitis and cellulitis will make amputation the issue. When the giant cell tumor is exceptionally large the best chance for a cure can be expected from a radical surgical procedure alone since neither curettage nor radiation can cope with the large mass.

In rare instances the histology of the tumor after curettage may appear suspicious enough to call for amputation. Problems in plastic surgery may come up after cure has resulted from curettage in some cases of giant cell tumor of the jaws.

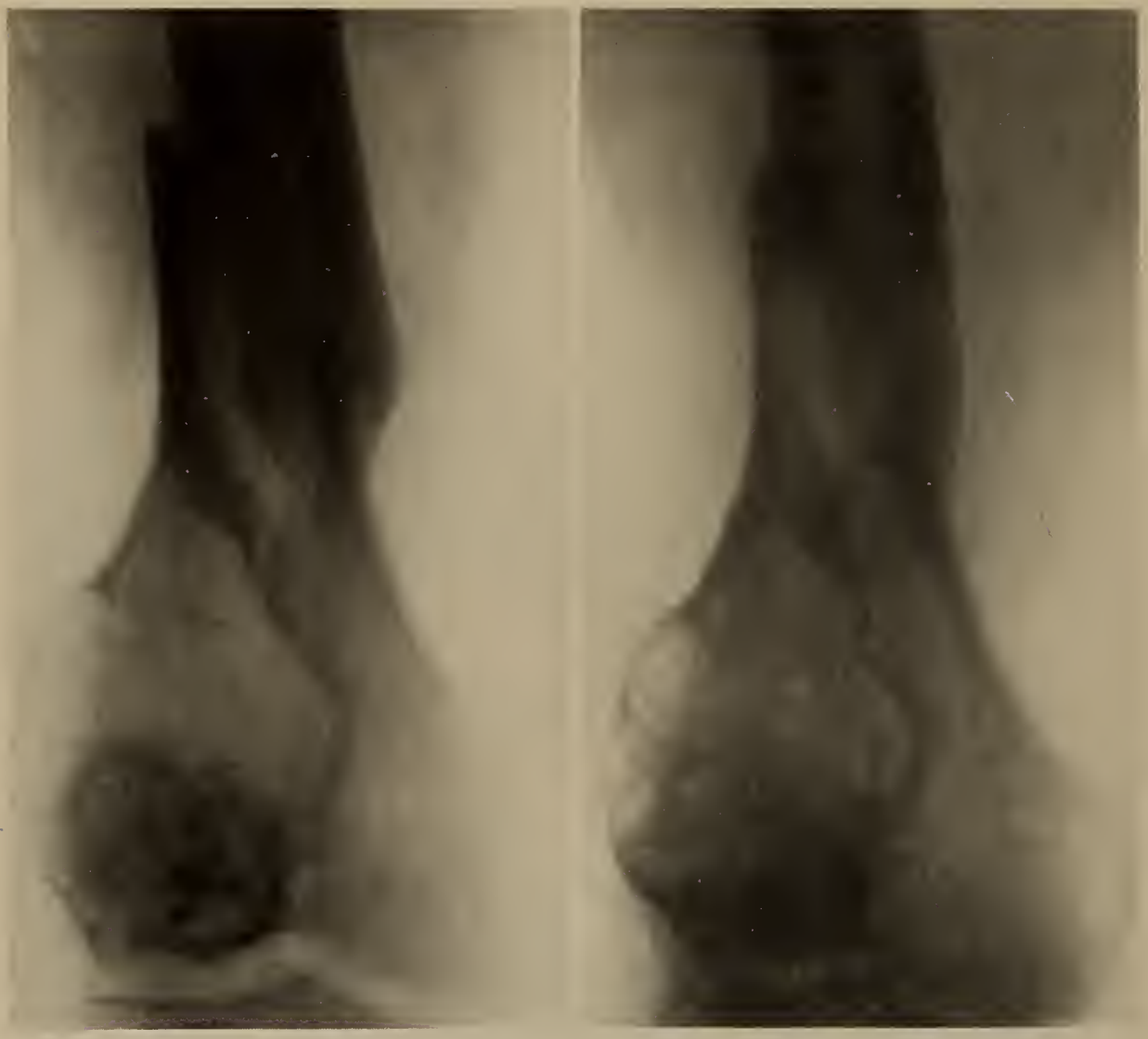


Plate 41. Courtesy Memorial Hospital, New York City. Giant cell tumor with a pathological fracture. Immobilization and radiation therapy instituted. The roentgenogram to to right was taken 22 months after the roentgenogram on the left. The function of the limb is completely restored.

Prognosis

In the preceding chapters I have attempted to stress the importance, in dealing with a giant cell tumor, of a combined evaluation of all data available. This is especially true in relation to prognosis. Only in the light of data accumulated from the clinical history, physical and radiological findings, and pathological examination may a prognosis be given. As in osteogenic sarcoma there are too few cases on record of the giant cell tumor being allowed to follow its natural course without interference by surgery or radiation for definite conclusions as to the natural outcome of such cases to be made. However, there is some evidence on hand to show that when left alone the giant cell tumor may follow one of two ways. Advanced growth of the tumor may lead to fatal hæmorrhage or septicæmia. Occasionally, following a pathological fracture or without it, such a tumor

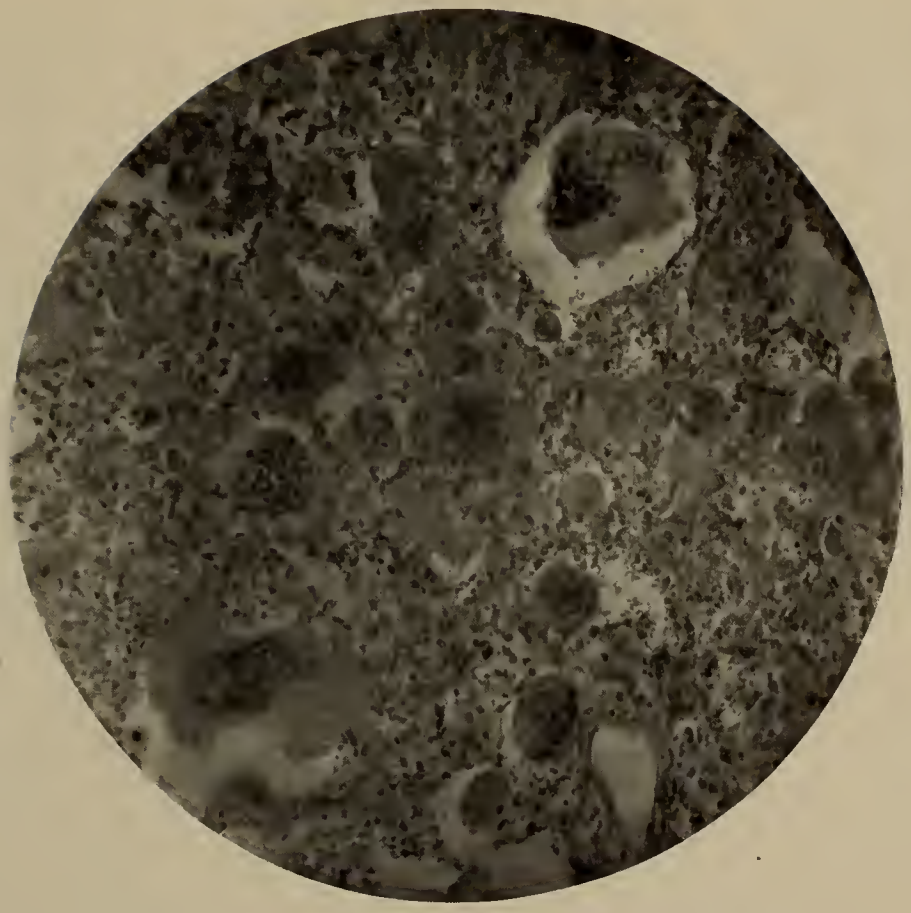


Fig. 103. Case 349. See Figure 104. Typical giant cell tumor of the tibia. The photomicrograph made from a section of tissue removed at the first operation (curettage).

may enter a cicatrizing stage in which the peripheral portion of the tumor is being converted into a dry, firm, fibrous tissue. The bony shell may become very thick. In the central portion, islands of active giant cell tumor will persist although some of them may degenerate and be replaced by cysts.

The question of the prognosis of giant cell tumor treated conservatively, by curettage or radiation, forms a subject for ardent discussion, and a voluminous literature has grown up about it which unfortunately is somewhat dogmatic on both sides. On one side many cases are cited of giant cell tumor leading to pulmonary metastases and death. Two sources of error of these authors are revealed by a careful study of these cases. The first is that not in all cases mentioned was the primary lesion a giant cell tumor and the second that not in all fatal cases are metastases proven to have been present. On the other hand the authors believe that giant cell tumor is always a benign lesion lacking the ability to produce metastases. The exceedingly few cases of giant cell tumor in which, after repeated surgical operations, pulmonary metastases and death occurred these authors explain by the fact that due to surgical insult and ill advised therapeutic measures the giant cell tumor became transformed into a malignant bone tumor which,

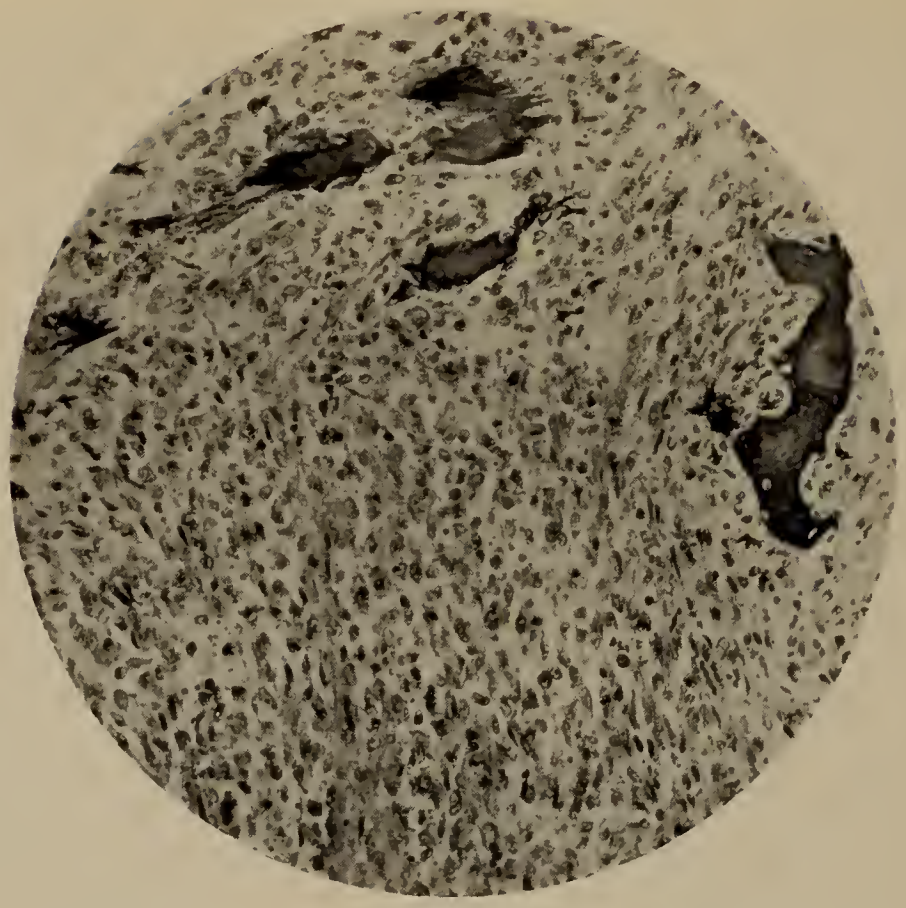


Fig. 104. Case 349. See Figure 103. Structure of the tissue removed from the leg amputated after repeated curettage operations. The histology resembles osteogenic sarcoma. Death with pulmonary metastases.

as a malignant tumor and not as a giant cell tumor, led to pulmonary metastases. It is obvious that such an argument is based solely upon technicalities which do not in the least change the fact that in a tumor diagnosed by experts as giant cell tumor the outcome was death due to pulmonary metastases. That giant cell tumor is essentially a benign lesion is generally conceded. It is benign in the oncological sense of the word although clinically it may offer serious surgical problems. The question as it stands today is whether or not a giant cell tumor is *always* benign. From the evidence on hand this question is to be answered in the negative. Giant cell tumor is essentially a benign condition and there is no case on record in which histologically a typical giant cell tumor gave pulmonary metastases of typical giant cell structure. In the few cases recorded in the literature of death following pulmonary metastases of a giant cell tumor, either both the primary lesion and the pulmonary metastases showed a typical giant cell tumor structure, or the primary lesion was a typical giant cell tumor but the pulmonary metastases were distinctly atypical for giant cell tumor histology. In exceptional cases a giant cell tumor may become a more malignant tumor as a result of repeated irritation—curettage and infection (Figs. 103 and 104).

The main rule that giant cell tumor is essentially a benign lesion is strongly supported by the fact that these exceptional cases are exceedingly rare; inasmuch as the possibility of forcing tumor cells into the blood channels during curettage is very great in so vascular a lesion. Cases have been seen of recovery following resection of a giant cell tumor which on dissection showed the presence of tumor cells growing in a vein. To produce metastases it is not sufficient to have tumor cells in the blood stream; the cells must be sufficiently viable to be able to settle down and to multiply at their new place. But when, after repeated irritations, the tumor cells become more resistant and viable they may acquire malignant features. This possibility that a giant cell tumor may become transformed into a malignant new growth is additional proof that at least in some instances giant cell tumors are true tumors and do not represent merely a repair reaction to inflammation.

The main factor in the clinical course of giant cell tumor requiring one to be on guard in the prognosis is rapid growth of the tumor. The typical giant cell tumor is of long duration and slow course. Rapidity of growth is a sign of aggressiveness of the tumor. Another reliable sign of aggressiveness is the destruction of a large portion of the bone shell of the tumor. The presence of the bone shell is important not because its absence is proof that the tumor has invaded the surrounding soft tissues but because destruction of the bone shell is in a moderately advanced tumor an indication of the aggressiveness of the new growth. A giant cell tumor reaching a very large size is very apt to recur after curettage since the size of the tumor excludes the possibility of a complete removal of the tumor tissue. With each recurrence the prognosis becomes less favorable. Care should be exercised in the arrival at a prognosis based upon a recurrence, because with each recurrence the growth is apt to become more anaplastic and malignant.

In relation to a prognosis the findings of a pathological examination are of outstanding significance. The giant cells of epulis type when present in excess are a true indication of the benignity of the lesion. The typical giant cell tumor where the giant cells form the bulk of the tumor is of very slow growth, not aggressive, and easily eradicated even by incomplete curettage. On the other hand with the disappearance of the giant cells and with an increase in the number of the spindle cells of the stroma the aggressiveness of the tumor increases. Viewed largely, the type of cells of the stroma is of greater importance than the giant cells. It is by the various numbers, sizes and shapes of the stroma cells that varieties of giant cell tumors are distinguished. Increase in the hyperchromatism of the stroma cell calls forth a warning as to the likelihood that a recurrence will take place after an incomplete surgical operation. A recurrence can be also expected when the stroma cells have become abundant and rounded. However, pleomorphism and cellularity in the central portion of a giant cell tumor

are not of such unfavorable significance for the prognosis as their presence in the peripheric portion of the tumor, where they notoriously mark aggressiveness. A guarded prognosis is to be given also in the case of the very vascular, so-called telangiectatic, giant cell tumor which as a rule is more aggressive and recurs more frequently than other types.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